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**KEOKUK, IOWA**







# SAJOUS'S ANALYTIC CYCLOPEDIA OF PRACTICAL MEDICINE

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VOLUME EIGHTEEN

SUPPLEMENT



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## PREFACE

THE constant aim of the Editors and Publishers of THE CYCLOPEDIA OF MEDICINE is to make it possible for every owner of the CYCLOPEDIA to keep abreast of the continuous progress in medicine with the least expenditure of time and effort at a minimum of expense. After much experience and careful consideration it was found that the most efficient and satisfactory way to accomplish this is to issue each year a Service Volume. This makes it possible to bring to the subscriber, in an easily handled, readily available, and concise form, a critical review of the noteworthy advances that occur in medicine, surgery, the various specialties and medical sciences each year. In this way the material found in the original contributions to the CYCLOPEDIA is kept thoroughly revised and up-to-date.

In order to render this Volume an authoritative work of definite practical value, the Editorial Board, which has been increased in size, has exercised the greatest care in the selection of a large group of contributors, all of whom are outstanding in their several special fields. These Reviewers have not attempted the impossible task of touching upon the entire medical literature of the past year, but have followed the much more serviceable policy of emphasizing primarily the subjects which are of evident importance or current interest and in which definite progress has been made.

The subject matter has been subdivided into the main divisions of Medicine, under which the various subjects and their subdivisions have been arranged alphabetically. About one-quarter of the Volume is devoted to internal medicine under which are included Allergy; Arthritis; Cardiovascular Diseases, with especial reference to disorders of the peripheral vessels; Endocrinology, marked by its many recent startling advances; Gastroenterology, including a discussion of vitamins and their deficiencies; Hematology and the newer concepts of diseases of the blood; Kidney Diseases; Disorders of Metabolism; Diseases of the Respiratory Tract; and Syphilology.

An adequate amount of space is given to Surgery which, in the main, is treated under the regional divisions of that subject. Ample attention has been given to a careful consideration of Abdominal Surgery in its various aspects, also to Pulmonary Surgery in connection with diseases of the lungs. The same is true of Surgery of the Central Nervous System, which is discussed under Neurology. A separate section is devoted to the newer aspects of Surgery of the Sympathetic Nervous System. Anesthesia, with especial reference to the recently perfected methods, is accorded a separate and important place. Cancer is extensively dealt with as is also the subject of Urology.

Surgery is followed by an extensive consideration of Gynecology and Obstetrics. The section devoted to Pediatrics is unusually complete and includes neurological and surgical conditions peculiar to children, as well as diseases of the newborn and infant feeding. The remainder of the Volume includes sections on Neurology, Ophthalmology, Otorhinolaryngology, Dermatology, Radiology, Clinical Pathology, and Therapeutics. Under this last heading not only the latest advances in Drug Therapy, but also Physical Therapy including Electrotherapy, Exercise and Manipulation, Fever Therapy, Ionization, Passive Vascular Exercise, and Ultraviolet

Radiation are fully treated, as is also, in a separate chapter, the fundamentally important subject of Dietotherapy. Throughout the Volume the question of treatment is stressed.

The success of such a volume as this depends for the most part upon the contributors who, in this instance, merit the thanks of the Editorial Board for their unfailing interest and coöperation. The Editor is deeply grateful to Dr. Edward L. Bortz, the Assistant Editor, who planned this work and so ably supervised its preparation. It gives the Editor much pleasure to once more express his thanks to Miss Louise I. Weisgerber for her valuable aid in the preparation of the manuscripts and the unusually complete index. The Publishers, who have been especially liberal in the matter of illustrations, are to be congratulated upon the excellent appearance of this Service Volume.

GEORGE MORRIS PIERSON.



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# The Cyclopedia of Medicine

## Revision Service - 1937

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### MEDICINE

Edited by GEORGE MORRIS PIERSOL, B.S., M.D.,  
and  
EDWARD L. BORTZ, A.B., M.D.

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### ALLERGY

By HARRY BOND WILMER M.D., and MERLE MIDDOUR MILLER, B.S., M.D.

**Sugar Metabolism.**—H. B. Wilmer, M. M. Miller and J. T. Beardwood (South. M. J. 29:197 (Feb.) 1936) have shown in the following treatise the carbohydrate mechanism and the alteration of this metabolism in allergic patients.

J. H. Black reported a series of 100 allergic cases on which blood sugar determinations were made. The majority had a fasting blood sugar of 70 to 90 mg. per cent. He performed a blood sugar tolerance test on himself (using 115 Gm. (38½ ounces) of glucose, *i. e.*, 1.75 Gm. (27 grains) per kilo (2½ lbs.) body weight) and found the following results: Fasting sugar 67 mg.; at the end of one-half hour, 114 mg.; 2 hours, 80 mg. Sugar tolerance tests on 12 other allergic individuals gave corresponding results. Black noted a marked sugar hunger in himself during an attack of hay fever and so also have the REVIEWERS observed in their patients a craving for sugar during a prolonged siege of pollen irritation. One patient stated he was able to eat as much as a pound of candy after dinner with no

untoward effects and with some definite therapeutic results.

Having been in touch with this work, and stimulated by the outstanding investigations of Long on carbohydrate metabolism, Wilmer, Miller and Beardwood (*loc. cit.*) began their research in sugar metabolism in allergic individuals. Injections of epinephrine produce hyperglycemia; parental insulin decreases the glucose in the blood.

Long, Lukens and Evans have shown that after the removal of both adrenals and the pancreas in cats, these animals have died of hypoglycemia in periods up to 28 days. Cats only depancreatized died of hyperglycemia.

It is believed that "there is some disturbance of carbohydrate metabolism in persons who have allergic manifestations. If it is not an altered carbohydrate metabolism alone, it may be the end-results of a glandular dysfunction that accompanies or is the back-ground of allergic disease."

Attention was called to the *association of allergy and diabetes*. In a group of 4762 allergic cases, only 2 had diabetes

or diabetic symptoms. One case did not show any evidence of diabetes until placed on moderately large doses of epinephrine at frequent intervals, when hyperglycemia ensued and was controlled by insulin therapy. Diabetes cannot be precipitated in experimental animals by epinephrine, but it is believed that this patient was definitely pushed into the diabetic state by the injections.

In studying 1870 diabetic patients, only 2 were found to be allergic. Occasional doses of epinephrine do not produce hyperglycemia, but it may be well to have sugar determinations at frequent intervals on patients taking this preparation over a long period of time.

The sugar tolerance test was done on 100 allergic cases. Since this report many more cases have been investigated in this manner, with corresponding results. All types of allergic patients were studied. The normal sugar tolerance curve is shown, also the sugar tolerance curve of a hay fever group, extrinsic allergic cases (sensitization to environmental atopens), and intrinsic allergic cases (no demonstrable sensitivity being found).

Glucose by mouth or intravenously is of questionable value in the treatment of *asthma*. **Epinephrine and glucose** together often give beneficial results, as there is less depletion of the liver glycogen if glucose therapy accompanies the epinephrine treatment. The REVIEWERS usually give 100 to 150 gm. ( $3\frac{1}{3}$  to 5 ounces) of glucose by mouth daily or 20 to 50 c.c. ( $\frac{2}{3}$  to  $1\frac{2}{3}$  ounces) of a 50 per cent. solution of glucose intravenously.

The following conclusions have been reached: The true etiology of allergic disease has never been discovered; the answer may be found in the opposing action or synergistic functional activity of all or of a group of glands; the glucose tolerance test is not pathog-

nomonic of allergic disease, but it is a valuable adjunct in diagnosis; carbohydrate tolerance and metabolism are altered in the allergic state; and, finally, the administration of glucose and epinephrine is of benefit in some refractory cases.

Since the above report, the REVIEWERS have reported a continuation of this work in a much larger group. This was given before the Pennsylvania Medical Society in October, 1936, and will be published in the Pennsylvania Medical Journal. This work is as follows:

It is still the belief of the REVIEWERS that carbohydrate tolerance and metabolism are altered in the allergic state, and this opinion is based on sugar tolerance studies of 513 patients.

The ability of an allergic patient to handle carbohydrate is best determined by the *sugar tolerance test*. Last year the findings in 100 personal cases were reported. These gave results almost identical with the investigator named above (Black). This laboratory evidence of an altered carbohydrate metabolism is, of course, not alone responsible for allergic manifestations, but may be the end-result of a glandular dysfunction that accompanies or is the background of this disease. The association of diabetes and allergy has been discussed above.

Kern has reported and the REVIEWERS have noted the high incidence of allergy in the offspring of diabetic parents.

Brady, in England, reported a series of cases having allergic manifestations who showed marked relief from the administration of glucose.

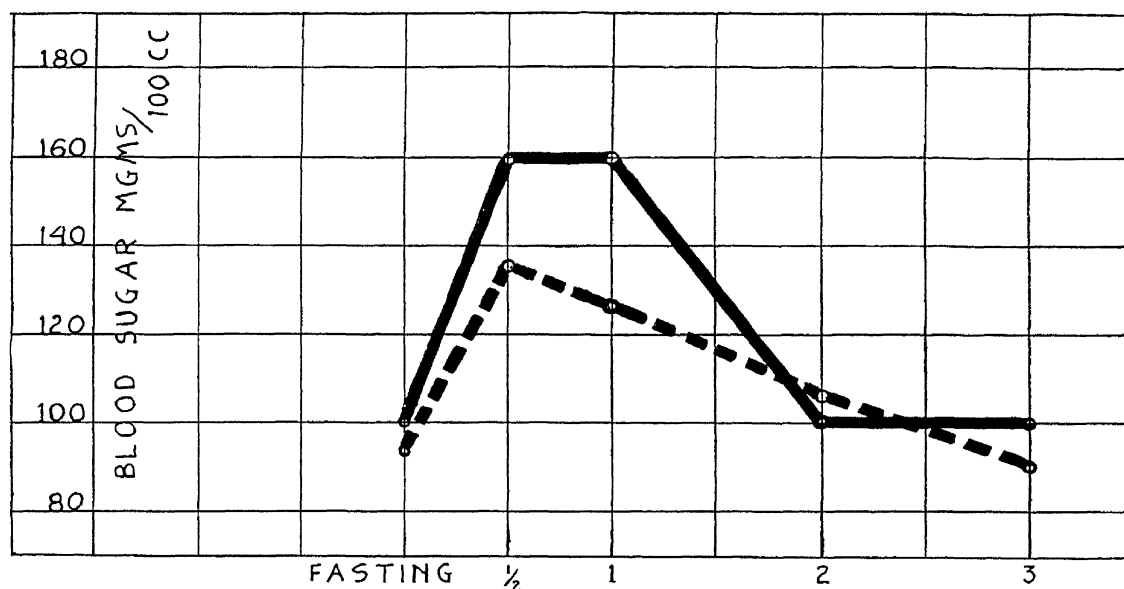
With these observations in mind, and having noted the therapeutic benefit from glucose by mouth and intravenously in refractory asthmatics, the work in carbohydrate metabolism in allergy has been continued.

GRAPH I shows diagrammatically the marked tolerance of allergic individuals in general for glucose. It is a composite diagram of all the types of allergic cases, asthma, hay fever, urticaria, etc.

GRAPH II shows more markedly the difference between the glucose tolerance curve in uncomplicated hay fever cases and in normal individuals. It is of interest to note in this group of highly sensi-

Attention is called to what the REVIEWERS believe is a significant finding in prolonged cases of asthma, *i. e.*, that the glucose tolerance curve during the acute paroxysms is very capricious and shift. They have shown this by repeated determinations on two very severe asthmatics. These readings, of course, may be due to any number of factors, too numerous to mention; one especially,

GRAPH I



— NORMAL SUGAR TOLERANCE  
 - - COMPOSITE GRAPH OF 633  
 SUGAR TOLERANCES IN PATIENTS  
 WITH ALLERGIC MANIFESTATIONS

tive, truly allergic patients, tolerance for sugar is highest of any classification.

GRAPH III shows the variation in the sugar tolerance curve in the intrinsic, mixed, and asthma type of allergic individual.

There is also shown diagrammatically in GRAPH IV the sugar tolerance curve in 32 cases of urticaria, 29 of perennial rhinitis and 21 cases of eczema. A corresponding difference in these and in the normal is noted.

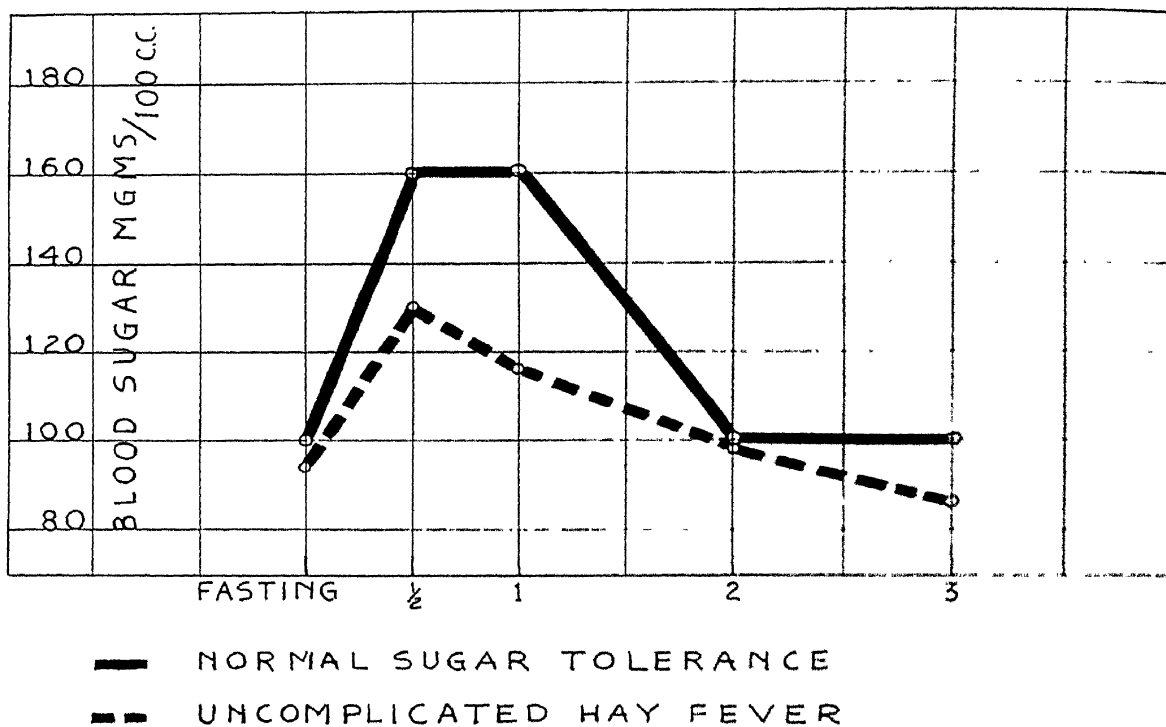
the prolonged use of epinephrine. As the patient's condition improves, his sugar tolerance curve more closely approximates the normal and, following complete desensitization, it is even more nearly the normal curve.

They feel that an allergic individual's carbohydrate metabolism is even more susceptible to extraneous disturbing influences than that of a normal person.

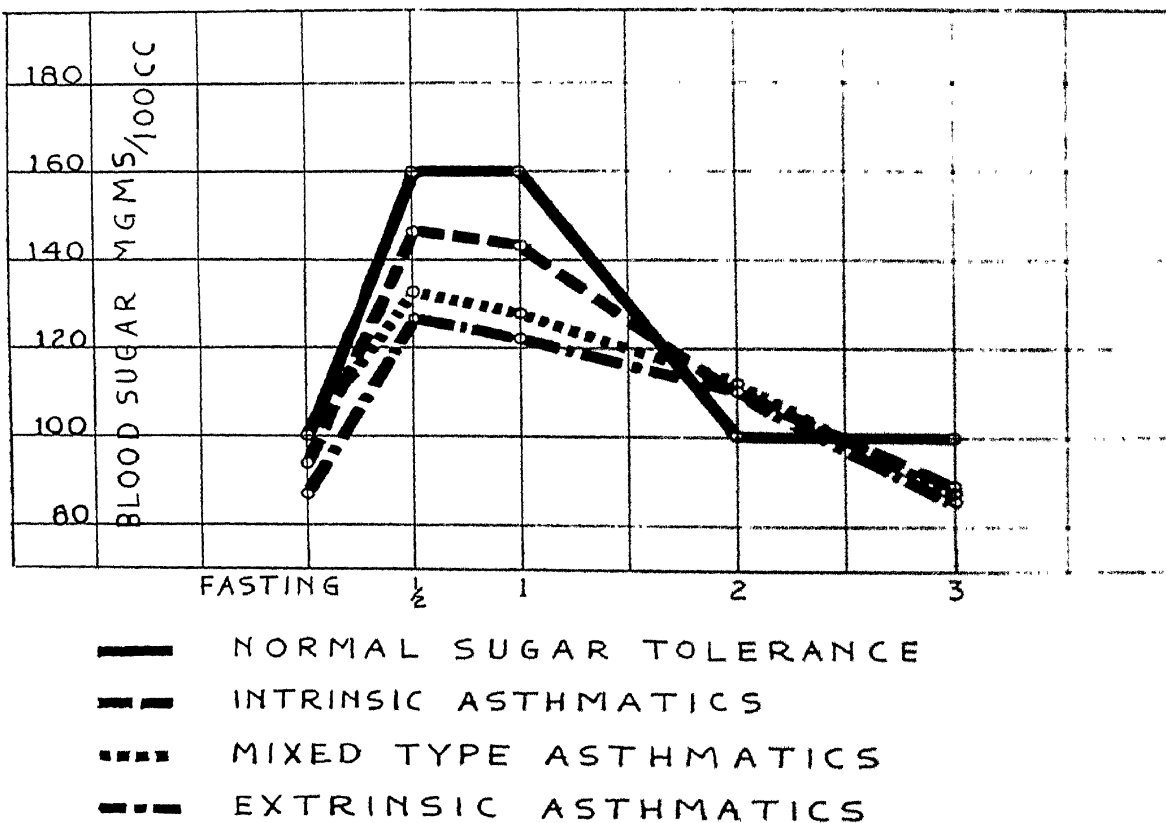
The glucose tolerance curve in 513 allergic patients is graphically shown,

## MEDICINE.

GRAPH II



GRAPH III



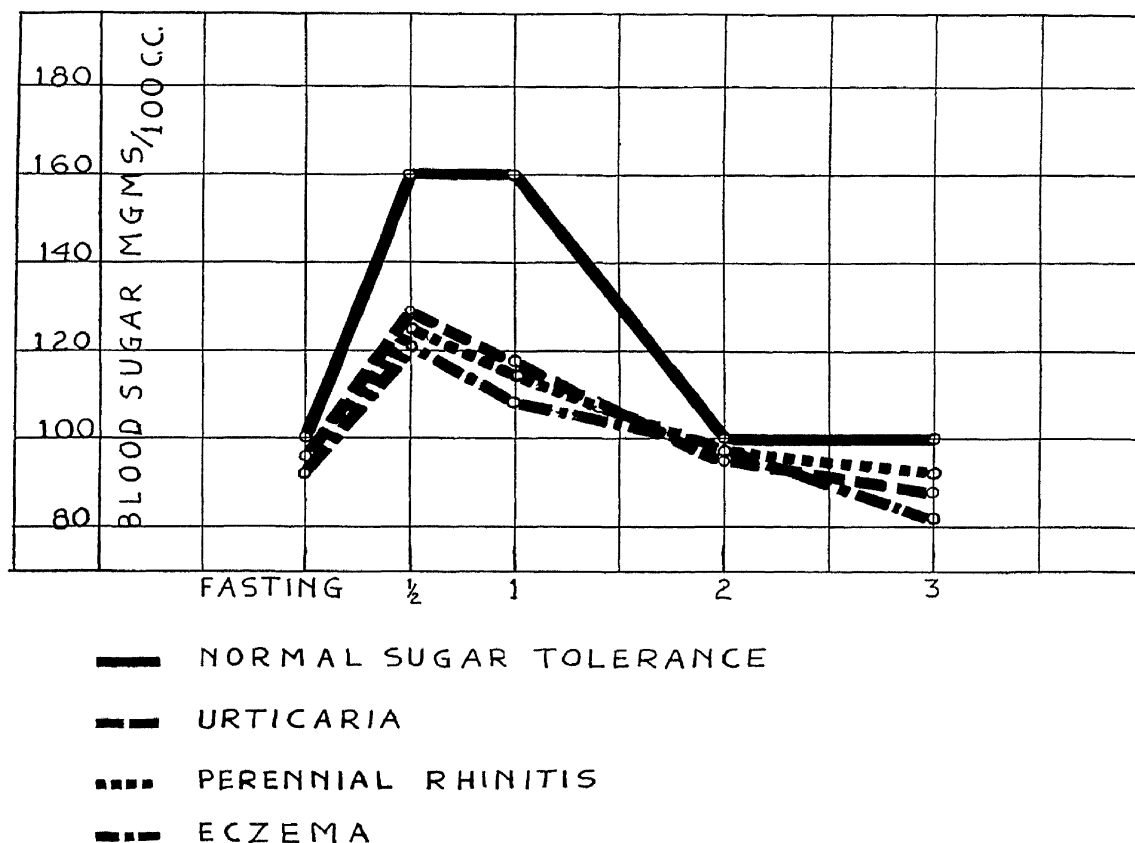
and a marked difference is noted between the determinations in this group and the normal group.

As the patient with allergic manifestations is put in such a state that his glandular and metabolic mechanism more closely approximates the normal, and as he improves clinically, his tolerance for glucose approaches the normal reading.

blood-pressure, asthenia, hypoglycemia, soft small pulse, and definite vasomotor instability; but there is no precise evidence that the adrenals alone are at fault.

**Treatment.**—CORTICAL HORMONE.—Since the REVIEWERS believe that hypofunction of the suprarenals is at least part of the picture in allergic disease, they have been actively treating patients with supplementary glandular therapy

GRAPH IV



The most sustaining evidence of an altered glucose tolerance with a definite tendency to a low curve in the allergic individual, is found in the following summary: In 633 glucose tolerance determinations done on 513 allergic individuals, only 1 patient was found to be diabetic with sugar in the urine. This is an incidence of .002 per cent. in comparison to .17 per cent. in normal persons

Allergic individuals often manifest all the evidences of hypoadrenia; low

during the past two years. First they used **cortical hormone** processed by the Swingle-Pfiffner method. The results, although at times most outstanding and spectacular, were by and large far from satisfactory and often disappointing. Tabulations of their findings in this form of treatment were presented last spring and showed 13 per cent. beneficial results in refractory cases. (H. B. Wilmer and M. M. Miller: J. Allergy 8:77 (Nov.) 1936).

Since that time they have been using extracts of the suprarenal gland by mouth. Two commercial preparations have been found most efficacious: **suprarenal concentrate** and **glycortal**. The dosage of each is 4 to 8 capsules daily.

Rogoff and Stuart, Harrop and Swingle, Pffner and Parkins, among others, have advocated the use of **sodium chloride** in adrenalectomized animals as an adjunct in maintaining life. Salt has been added as a supplementary means in patients with symptoms simulating a profound hypoadrenia.

The REVIEWERS do not believe that the use of adrenal extracts of the type available at present and the addition of glucose and sodium chloride have any marked specific effect on the symptomatology of allergic disease, but a definite, progressive and gradual increase in weight in these asthenic individuals was noted. This corresponds with the findings of Hoskins. Also, the patients' general resistance seemed to improve and a marked feeling of well-being was observed.

The use of adrenal extracts, sugar and sodium chloride, does not replace the usual extant methods employed in the treatment of allergy. **Elimination, desensitization, and immunization** are still the fundamental methods of allergic therapy, but the above-named preparations are basic adjuncts in the armamentarium. It is believed that they help reinforce the primary background of endocrine and nervous stability that is so often lacking in the allergic individual.

At present, if an allergic patient manifests the clinical symptoms of hypoadrenia, no matter whether this state may be due to a primary hypersensitive background, or the result of long-standing debilitating illness, whatever the source may be, he is put on a regimen approximately as follows:

#### *Therapeutic Regimen in Allergy.*—

1. **Elimination of offending atopens.**

2. **Hyposensitization** for those proteins which cannot be removed from the patient's environment.

3. **Suprarenal concentrate**, Gr. 2 (0.13 Gm.) capsules, 4 to 8 daily, or tablets of **glycortal**, 4 to 8 daily.

4. If the patient's carbohydrate mechanism is such that he shows a low sugar tolerance curve with a high tolerance for glucose, he is given  $\frac{1}{2}$  ounce (15 Gm.) of powdered **dextrose** in fruit juice at the periods in the day when his blood sugar should be at its lowest ebb, *i. e.*, at the end of the morning, afternoon, and at bed-time.

5. **Vitamin** products such as **cod-liver oil**, **viosterol**, etc., are also very necessary adjuncts.

6. Drug therapy as indicated for prophylaxis and relief.

This whole regimen has been found most essential, especially in refractory cases. This is not the extent of the treatment employed, as many other measures may be indicated. These are individual in each case.

**Endocrine therapy** is often of extreme importance, especially in patients at the menopause. Preparations containing **female sex-hormone** are often indicated in cases with *complications associated with menses* and the *menopause*.

Investigations of all systems and mechanisms of the body have thrown no light on the true etiologic background of allergic disease. This fundamental condition from which allergy inevitably follows must be found before there can be any marked advance in therapy. In the opposing action or synergistic functional activity of any one or group of glands may be found the answer. It is hoped that future investigation may reveal this exact mechanism.



NASAL IONIZATION.—H. O. House and L. N. Gay, (J. Allergy 7: 86 (Nov.) 1935) report the results obtained from nasal ionization. Twenty patients were treated by the method of Warwick and his exact technic was used. Fifteen patients had allergic nasal conditions and 5 nonallergic. In this latter group, 3 were improved, 1 was unimproved, and 1 was worse. Of the 15 allergics, 3 were improved, 7 were unimproved, and 5 were worse.

*Untoward symptoms* were encountered with varying degrees of severity. Nasal discomfort, obstruction and headache were the most important side reactions. Seven suffered severe reactions with nasal distress accompanied by asthma. This lasted in several cases for a week or longer.

In conclusion, it has been decided that this method was helpful in several of the group with *nonallergic rhinitis*. It was of no aid in the allergic group. The procedure often caused great discomfort and at times asthmatic seizures. In conditions of hypersensitiveness it should not be given any consideration.

This same phenomenon or procedure was investigated and reported by H. L. Alexander (*Ibid.* 7: 87 (Nov.) 1935). It has been pursued by him at the Washington University Medical School from two angles: a study of the mechanism and a clinical analysis of cases treated. The theories as to the reaction that occurs are many and varied but no conclusion has been definitely reached. Histologic examination of the ionized mucous membrane shows signs immediately following treatment of an acute inflammation. A small amount of fibrosis, which is not enough to interfere with function, is usually present. Each ionization, however, increases the amount of fibrosis so that, if done often, there is certain definite risk of future damage.

From the clinical standpoint, the following results were found: *Hay fever* patients ionized before the season did poorly. If performed late in the season, the effect may last to the end. In the great majority of cases hypersensitization with pollen extract is a far superior method.

In *vasomotor rhinitis* when there is a marked hypersensitivity, the results are discouraging and relapses occur. In the group with *no specific sensitization*, ionization has a place because in some cases the patients were entirely free for a year.

In *asthma*, *vasomotor rhinitis*, *migraine* and *vernal catarrh*, success has been claimed but, in general, ionization has done no good.

From these observations it has been found that the exact mechanism in this procedure has not been discovered. Clinically, it is an inferior form of allergic therapy in asthma, hay fever, etc. It seems to have a definite place only in certain cases of vasomotor rhinitis without an established and specific etiology.

REST.—B. A. Credille (J. Allergy 8: 71 (Nov.) 1936) stresses the importance of **rest** in the treatment of allergic diseases. Fatigue and exhaustion are very vital secondary factors, and as has been found, often the most important mechanism in precipitating an attack.

He believes that an allergic individual has a definite fatigue threshold. When this is lowered, the patient is more likely to have an attack.

Prolonged rest is a most valuable adjunct in the treatment of *asthma*, *asthmatic-bronchitis* and the like. This is especially true of "high strung" and nervous patients.

A hospital is the ideal place for complete relaxation and rest. It has been the writer's experience in many cases that hospitalization *per se* was enough

to give a patient complete relief, without any medication, desensitization, etc. Improvement practically always follows continued rest. Complete rest is the first and most important part of any acute asthmatic's regimen. Rest must be both mental and physical.

GENERAL TREATMENT. — L. Unger (South. M. J. 28:35 (Jan.) 1935) stresses several important observations on the make-up and characteristics of an allergic individual. Every part of the body from the brain down may become sensitized at one time or another.

The allergic person is a peculiar individual, constitutionally different from the normal man or woman or child. He is hypersensitive and reacts to substances that do not affect normal people. Any protein may be the activating agent or atopen. The condition is hereditary in 60 to 70 per cent. of cases and probably more if all histories were accurate.

The patient who is allergic is markedly susceptible to environmental influences and changes which have practically no effect on the normal individual. These are usually contributory factors, but the underlying hereditary constitution, specifically or otherwise hypersensitive, must be present before these extrinsic influences can prevail.

The treatment of *bronchial asthma*, as previously shown, is divided into 2 stages: (1) the management of the acute attack, and (2) prophylaxis, both specific and nonspecific. These phases have been considered previously but, in general, **elimination** of the offender is ideal and, if this cannot be done, resort must be had to **desensitization** or **hyposensitization**. This consists of an attempt to increase the resistance of the patient to a substance or a group of substances to which he or she is sensitive. Hereditary sensitivity has long been recognized, but the atopen is a matter of chance.

Food desensitization by mouth in gradually increasing doses is very tedious and difficult and results are at times very disappointing. Hyposensitization by injection of animal danders, dust, and pollen is, in the majority of cases, quite successful and untoward reactions are becoming much less frequent.

A few salient points in the treatment of the attack are:

1. **Epinephrine (adrenalin)** 1:1000 dilution in doses of 5 to 15 minims (0.3 to 1 c.c.), is the drug of choice and may be repeated at frequent intervals. It is magic at times, but often feeble in an old chronic asthmatic. It is not habit-forming and usually no permanent damage is encountered from its use. It must be given as early in the attack as possible and, given at regular intervals, *i. e.*, every 2 hours for 24 to 48 hours, it often seems to build up an adrenalin reserve. It may be given more frequently if the occasion arises.

2. **Ephedrin** may be given by mouth, but is efficacious in mild cases only.

3. Synthetic ephedrin preparations, **propadrin**, etc., are of some benefit in very mild cases and they do not usually give the unpleasant side effects of ephedrin.

4. **Morphine** should not be used in acute asthma unless epinephrine has failed and when given, morphine should be tried very cautiously and in  $\frac{1}{8}$  to  $\frac{1}{6}$  grain (0.008 to 0.01 Gm.) doses. Many asthmatics have an idiosyncrasy to morphine and other opiates. Often morphine gives the rest needed by an asthmatic and may have to be used. **Pantopon** and **dilaudid** are often of benefit.

5. **Atropine** gives bronchial relaxation and dilatation but, at times, has an unpleasant drying effect on the secretions and renders the tenacious mucus in an asthmatic chest even more mucilaginous.

6. In refractory cases and in acute attacks, the REVIEWERS have found **glucose** intravenously in doses of 20 to 50 c.c. ( $\frac{2}{3}$  to  $1\frac{2}{3}$  ounces) of a 50 per cent. solution of untold value. It may be given from every 4 to 6 hours to once daily until the patient is well able to take sufficient carbohydrate by mouth.

7. **Potassium iodide** in doses of 5 to 15 grains (0.3 to 1 Gm.) 3 times daily is probably the best alterative and liberator of bronchial secretion at present available. Some allergic individuals cannot tolerate therapeutic doses, but it is worth a trial in all asthmatics, especially of the intrinsic or mixed type.

8. Any **endocrine preparations** indicated may be the corrective influence that will solve the whole problem in some allergic individuals. Each case is a problem in itself and all surgical, medical and endocrine problems must be corrected before complete and continued relief is experienced.

**ASTHMA.—Treatment.** — Beneficial results were obtained by J. B. Graeser and A. H. Rowe in the treatment of bronchial asthma by the **inhalation of epinephrine** solution, 1:100 dilution. For the **spray**, an atomizer should be used that vaporizes the solution to a sufficient degree so that it will be disseminated to all parts of the lungs. A glass atomizer that delivers an even vapor-like spray has been perfected. The use of an inferior atomizer may produce unpleasant and annoying dryness of the throat and, at times, gastrointestinal upsets from contact of the strong solution with the various mucous membrane surfaces.

The *dosage* varies with the patient and it is a trial and error method at the beginning. Caution must be observed, although the untoward effects noted in giving the 1:1000 solution hyperdermi-

cally have not occurred. In several patients a severe headache has been noted to follow prolonged use. It is well to allow a few minutes to elapse between several deep inhalations.

In a great many instances the use of the 1:100 solution by inhalation has supplanted the hypodermic injections of the 1:1000 solution. As a *prophylactic* measure, it is suggested that repeated inhalations during the free period of the day may prevent the recurrent attacks or mitigate the severity of the ensuing paroxysm. Other investigators have found the use of adrenalin by inhalation very successful.

C. K. Maytum and E. T. Leddy (J. Allergy 8: 66 (Nov.) 1936) have treated 23 asthmatics with **x-ray therapy**. These patients were all refractory to other methods of treatment. This series of cases included all types of asthma and was not a selective group.

Irradiation of the mediastinum through 2 paravertebral fields seemed to give less gastrointestinal reaction than the anterior-posterior cross-fire. If no contraindication exists and the patient is able to be prone without discomfort, the treatment is given over the mediastinum from the rear, ascending to the following formula:

|                |                  |
|----------------|------------------|
| K. V. ....     | 135              |
| Filter .....   | 6 mm. A L        |
| Distance ..... | 40 cm.           |
| Time .....     | 22 to 26 minutes |

One treatment usually suffices for a time, but may be repeated at intervals if absolutely necessary.

The mechanism of relief is not known, but as Desjardins has reported, is probably due to a decrease in the secretory power of the mucous glands in the trachea, and probably a liberation of antibodies, due to the destruction of leukocytes, and also a stimulating effect on the production of eosinophiles.

The workers believe that x-ray therapy is a definite adjunct in the treatment of asthma, and its most important benefit is in its ability to interrupt the cycle of paroxysmal attacks.

**HAY FEVER.—Treatment.**—A. Vander Veer (J. Allergy 7: 578 (Sept.) 1936) reports a study of the relative merits of the *seasonal and perennial treatment* of hay fever. At present there is a great deal of controversy among allergists as to the better type. This article deals with observations on an average of 430 patients annually from 1930 to 1934. A questionnaire was sent to each patient, who alone evaluated the results obtained.

According to the chart published in the résumé, it was shown that the perennial results were uniformly better by 8 to 10 per cent. than the seasonal. This is according to statistics, but the human equation must be brought into the picture. It is much easier to persuade a patient with complete relief to continue throughout the year than one who has been refractory to the seasonal injections. This factor may tend to place more of the satisfactory cases in the perennial group.

There are two disadvantages in perennial treatment. Many patients forget to take the injections and if an interval of 5 weeks has elapsed, the risk of a constitutional reaction is increased. Also, there is always the possibility of a patient becoming saturated and into such a state that very small injections will give constitutional reactions.

Vander Veer considers that perennial treatment is more likely to produce a permanent cure eventually than the other methods.

In general, the problem is best solved by choosing the right method for each individual patient, depending on temperament, sensitivity, and previous results

obtained. The preseasonal and coseasonal methods of treatment are quite necessary in many cases but, under ideal conditions and when there are no untoward symptoms, it is felt by a great many allergists that the perennial treatment is, by and large, the method of choice.

**INSULIN ALLERGY.**—A very complete review of the literature on insulin allergy is given by M. T. Davidson, and a case of hypersensitivity is reported.

Early in the treatment of diabetes with insulin, many reactions occurred. Most of those reported were local, but there was a small percentage of constitutional reactions. Most of the untoward effects were produced by the extraneous protein which carried the insulin, *i. e.*, beef, pork, or other animals.

The manufacture of insulin has been greatly improved. The end-product is highly refined and most of the extraneous material has been removed. It has been shown in a number of cases that the offending protein is crystalline insulin, which probably is not the same protein as human insulin.

Tuft reported 2 cases in 1928, one due to extraneous protein and the other to insulin itself. Allan and Scherer reported 100 cases in 1932, 84 of which were mild local reactions. The local as well as the systemic reactions were of varying degrees. The constitutional manifestations may be urticaria, angio-neurotic edema, asthma, or any of the other allergic responses.

Many other cases of varying severity have been reported from time to time. The incidence of constitutional reaction is comparatively rare and a great many of the local reactions have been reported as clearing up spontaneously.

The most usual constitutional manifestation is urticaria. In a case reported by this author, it was found that the

patient was sensitive not only to beef and pork insulin, but also to crystalline insulin. Very marked and severe urticaria was the rule after injection of insulin. This symptom was usually relieved by adrenalin and ephedrine. If the diabetic condition had persisted, desensitization was contemplated by the method of Besredka and Gloyne for use in horse serum sensitivity cases. An attempt at passive transfer gave negative results.

J. A. Murphy, J. T. Beardwood and M. M. Miller (*Ibid.*) reported 2 cases of insulin hypersensitivity manifesting itself by generalized reaction, one as urticaria and the other as an asthmatic seizure. The one patient was definitely allergic and the other was not. The percentage of local reactions is believed to be relatively higher, but only 2 cases of generalized reaction due to insulin hypersensitivity were found in 940 cases using insulin in the treatment of diabetes.

The first case presented reacted to all types of commercial insulin for which she was tested, with major reaction to crystalline insulin. Fortunately, this patient's condition was readily controlled by diet, so that it was not deemed necessary to desensitize her to relieve the symptoms and signs. There was no previous personal history of allergy and no hereditary history of allergy in the family.

An attempt at passive transfer was done both in a diabetic and a normal individual. Both attempts were not sufficiently positive to indicate that the transfer had been successful.

In the second case, it was discovered that the patient had previously suffered with fairly severe bronchial asthma. Her insulin hypersensitivity manifested itself as an attack of asthma. The insulin used had been obtained from pork.

This patient was skin-tested on 2 occasions about a month apart and she

reacted to all types of insulin by the intradermal tests. She also reacted to pork protein, but not to beef protein. After being placed on beef insulin, she had no untoward reactions.

Both cases reported had reactions from injections of insulin. The one developed urticaria; the other asthma. One case was a known allergic; the other was not. Both had had previous insulin injections. A change of the source of insulin proved helpful to one but not the other.

**SURGERY AND ANESTHESIA.**—R. Andre and R. C. Grove report a survey of a group of 204 allergic patients who had nose and throat surgery under general anesthesia. Their findings are most important, as the allergist and rhinolaryngologist are confronted with two problems: (1) When to operate on an allergic patient, and (2) what type of anesthesia to use.

It has been found from observation of this series that general anesthesia is safe in allergic patients. It may even be used in the severe asthmatic if the case is carefully selected and prepared. A method which employs small amounts of anesthesia with carbon dioxide and oxygen hyperventilation is found to be the one of choice. In this group, pulmonary complications were noticeably absent.

H. Schenk, in discussing this paper, states that from the conclusions in this study it would seem that general anesthesia is as safe in allergic patients as in others. He cautions that the anesthetic and operation should not be entrusted to average operators and anesthetists. It is most necessary that all patients be subjected to painstaking preoperative treatment and the proper attention must be given to basal anesthesia and hyperventilation at the close of the operation. **Avertin** has been used

successfully by the above authors and has been found satisfactory by others.

Many *operations on the upper respiratory tract* in allergic patients can and should be done under **local anesthesia**. This again calls for selectivity of cases as to temperament and physical condition. Schenk advises the use of local anesthesia in the radical operations of the Caldwell-Luc and the Ferris Smith types. This is suggested because it

minimizes shock and gives the operator a dry field of operation.

A great deal may be said for both types of anesthesia, but the importance of the correct selection of cases for each form must again be emphasized. Whether the operation is done under local or general anesthesia, the pre-operative care and postoperative management assume rôles of extreme importance.

## ARTHRITIS AND RHEUMATOID CONDITIONS

By RALPH PEMBERTON, M.S., M.D., and C. W. SCULL, M.S., Ph.D.

**Introduction.**—Knowledge regarding rheumatoid disease has advanced along several fronts during the past few years. Scrutiny of recent data indicates that rheumatoid disorders are widespread in occurrence and constitute an economic and social problem of the first importance in many countries. Investigations of the *etiological factors* have stressed the significance of divers influences upon these syndromes, particular emphasis having been placed upon indirect evidence of infectious factors in atrophic arthritis and upon age and trauma in the production of hypertrophic arthritis. Experimental efforts to duplicate in joints the pathological processes characterizing clinical varieties, have indicated that various kinds of factors lead to the production of articular pathology. These agencies include not only irritants of bacterial origin but also simple compounds and nutritional deficiencies. Studies of joint *pathology* have emphasized the important relation of the reticulo-endothelial system and the lymphatics as portals of entrance and exit from the joint tissues. The limited capacity of the central portions of articular cartilage for regeneration has been demonstrated. New methods of *therapy*,

including physical measures and drugs, have been advanced. Experience with such measures has demonstrated the necessity for placing chief reliance upon broadly active measures such as **rest, nutrition, control of infections, orthopedic and simple physical measures.**

A partial measure of the extent of current literature bearing upon arthritis and allied rheumatoid states is indicated by the fact that the library of the *Ligue Internationale Contre le Rhumatisme* containing 5156 items has been augmented by upwards of 600 new titles during the period from May, 1935, to May, 1936. These titles representing books, papers and reports upon various phases of rheumatism, constitute but a fraction of all the items appearing in the widely scattered medical journals which carry articles upon related topics.

National committees for the study and control of rheumatism have been organized in twenty-four countries and during the past year (1936) five more have been formed. These groups co-operate within the *Ligue Internationale contre le Rhumatisme*. The Bureau d'Hygiene of the League of Nations at Geneva has sought and obtained the collaboration of the *Ligue* in "The Campaign Against Rheumatism" (Quart.

Bull. Health Organ. League of Nations 5:237 (June) 1936)

**Nomenclature and Classification.**—

Rheumatoid states encompass a wide range and variety of disorders. While we are primarily concerned here with the large groups comprehended under atrophic and hypertrophic arthritis, it is essential to contrast and compare these syndromes with other diseases, involving articular tissues, in order to approach a practical perspective of the field. As new data appear from the scrutiny of patients, nomenclature and classification are modified or revised. In view of the growing recognition of the fact that various kinds of injurious influences evoke responses upon the part of joint tissues which are pathologically similar, there is a trend toward an expansion of nomenclature to describe rheumatoid diseases, not only according to the ultimate pathological appearance, but also according to the predominant clinical symptoms and/or apparent etiologic factors. Two typical schemes embodying these considerations which are in current use are presented.

A system provisionally adopted by the *Ligue Internationale contre le Rhumatisme* (Report of Secretary (July) 1936) for use in the compilation of comparative statistical data upon rheumatoid disorders follows:

Group A.—

1. (a) Rheumatic fever.
- (b) Sub-chronic rheumatic arthritis.
2. Peliosis rheumatica, purpura rheumatica, chorea, erythema nodosum, morbus maculosis.

Group B.—Non-articular manifestations:

3. Muscular rheumatism, myalgia, fibrositis, pleurodynia, torticollis.
4. Lumbago.
5. (a) Sciatica, ischias.
- (b) Other types of neuritis.

Group C.—Chronic joint change.

6. Rheumatoid arthritis—atrophic arthritis.

7. (a) Osteoarthritis—hypertrophic arthritis.
- (b) Spondylitis deformans.
8. Chronic gout.
9. Chronic changes, unclassifiable.

P. S. Hench and others (Ann. Int. Med. 8:1315 (Apr.) 1495 (May) 1935) suggest the use of the following working clinical classifications based upon presumptive causes or characteristics, with particular emphasis upon those manifestations which are chiefly intra-articular and those which are predominantly extra-articular.

| <i>Principal Etiologic Factors</i> | <i>Principal Characteristic of Lesions</i> |
|------------------------------------|--|
|------------------------------------|--|

- |  |   |
|--|---|
| <p>I. Trauma:</p> <p>(a) Extrinsic (exogenous):</p> <p>Acute.</p> <p>Occupational.</p> <p>(b) Intrinsic (endogenous):</p> <p>Chronic.</p> <p>Postural, static.</p> | <p>Intraarticular:</p> <p>1. Traumatic arthritis.</p> <p>2. Traumatic synovitis</p> <p>Extraarticular:</p> <p>1. Traumatic fibrositis.</p> <p>2. Traumatic bursitis.</p>  |
| <p>II. Specific infections:</p> <p>Generally acute; may be chronic.</p>  | <p>1. Gonorrheal.</p> <p>2. Tuberculous.</p> <p>3. Septic staph., Strep.</p> <p>4. Pneumococcal.</p> <p>5. Typhoidal.</p> <p>6. Syphilitic.</p> <p>7. Miscellaneous: Malta fever, dengue, dysentery, leprosy, yaws, malaria, diphtheria, influenza, meningococci.</p> <p>Extraarticular:</p> <p>1. Fibrositis, trichinosis, psoas abscess.</p> <p>2. Bursitis, syphilitic.</p>  |
| <p>III. "Nonspecific" infections, possibly related to streptococcic infection or toxins.</p>   | <p>Intraarticular:</p> <p>1. With rheumatic fever.</p> <p>2. With specific ulcerative colitis.</p> <p>3. With scarlet fever.</p> <p>4. With skin diseases, psoriasis, erythema nodosum, scleroderma, lupus erythematosus, peliosis rheumatica.</p> <p>5. Atrophic arthritis, including atrophic spondylitis.</p> <p>Extraarticular:</p> <p>1. Infectious fibrositis.</p> <p>2. Rare forms of myositis, fibrosa, ossificans.</p> |

- IV. Degenerative tissue change.
- Intraarticular:
1. Hypertrophic (senescent).
  2. Arthropathies:
    - (a) Charcot's joints.
    - (b) Pulmonary osteoarthropathy.
- Extraarticular:
1. Fibrositis.
  2. Bursitis.
- V. Chemical.
1. Probably chemical:
 

Intraarticular:

    - (a) Gout.
    - (b) Hemophilia.
    - (c) Serum sickness.
    - (d) With ochronosis.
    - (e) Acromegaly:
 

Essentially osseous.
    - (f) Parathyroidism:
 

Essentially osseous.
  2. Possibly chemical:
    - (a) Intermittent hydrops.
    - (b) Allergic — from food.
    - (c) Climacteric.
    - (d) Endocrine:
      - (1) Ovaripriva.
      - (2) Thyreopriva.
- Extraarticular:
- Myalgias with lead, thyroid, alkalies, bismuth, arsenic, fatigue products.
- VI. Neoplastic.
- Intraarticular:
1. Primary (Chondromatosis).
  2. Secondary (Sarcoma).
- VII. Miscellaneous:
- Intra- and extra-articular:
1. Mixed.
  2. Unclassifiable.
  3. Functional, hysterical.
  4. Congenital anomalies.

**Incidence and Social Cost.**—The general incidence of rheumatoid diseases in the United States has been estimated by M. F. Lautman ("Arthritis and Rheumatic Diseases," McGraw-Hill, New York, 1936) to include 2 to 3 million persons. The average charge for medical care per case of rheumatism has been estimated by T. Parran (The World Today 4:25 (Dec.) 1936) to be \$30.52 per year. The national medical cost occasioned by these diseases calcu-

lated upon these data would appear to be in the neighborhood of \$95,000,000 annually. In estimating the total economic waste of these diseases, it is proper to add that due to loss of producing hours and education. Lord Herder (J. Lab. and Clin. Med. 22:12 (Oct.) 1936) states that more working hours are wasted in Great Britain through chronic rheumatism than through any other disease.

A survey of the relation of housing to the problem of rheumatism, especially as regards the juvenile variety, leads F. J. Poynton (Acta Rheumat. of 8:48 (Aug.) 1936) to the conclusion that poor housing constitutes one feature of poverty which, although not primarily etiologic, tends to make the disease become chronic in many instances. Draughts, dampness and sudden decreases in temperature are among the features involved in improper housing which are believed to encourage the development of chronicity in fibrositis and other forms of rheumatism. A study of the relative geographical distribution of 10,000 cases of rheumatic disorders in Oslo, Norway, made by J. Reinhardt-Natwig (*Ibid.* 8:50 (Aug.) 1936) reveals a marked tendency to a concentration in certain streets. In 7 streets there were 5.7 to 7.9 per cent. of the adult population suffering from rheumatism.

The fact that certain rheumatoid disorders tend to appear more frequently among certain occupational groups is pointed out by J. Teisinger (*Ibid.* 8:55 (Aug.) 1936), who notes that shoulder disability is frequent among workers subjected to exceptional exertion and to exposure. R. J. Weissenbach and R. Merklen (*Ibid.* 8:57 (Aug.) 1936) found that sedentary workers may suffer rheumatic afflictions partly conditioned by lack of exercise.

**Etiology.**—Many factors contribute to the production, and condition the



course of chronic arthritis and, by virtue of this, must be evaluated in any consideration of etiology. Newer work has served to reemphasize this situation. Among such factors, the relative importance of which appears to vary in different individuals, are included heredity, constitution, body build, sex, age, trauma, infection, parasitism, allergy, fatigue, exposure to cold and damp, endocrine dyscrasias, nutrition, disturbances of intestinal, circulatory, respiratory and nervous systems.

R. L. Haden (J. Lab. and Clin. Med. 22:1 (Oct.) 1936) has restated the fact that the majority of cases in the group of rheumatoid diseases arise from factors which are either unknown, non-specific, or both. Infection by some unidentified bacterium or filterable virus is held to be important in atrophic or rheumatoid arthritis, whereas aging or disturbance of the nutrition of cartilage is thought to be more important in the etiology of hypertrophic or degenerative arthritis. There are numerous precipitating factors which profoundly modify the influence of the causative agents, without which such agents might not become active, including particularly exposure to cold and damp, specific infections, chronic focal infections, undernutrition, toxemia, diminished blood flow and exhaustion. By the same token there are many accelerating factors which make the physiologic age of tissues, including those of joints, exceed the chronological age of the patient and hence contribute to the production of hypertrophic arthritis, including especially: abnormal metabolism, trauma, disturbance in circulation, toxemia, nutritional deficiency, gastrointestinal disturbances, and exhaustion.

Additional data regarding the "soil" upon which arthritis may develop is presented by J. Kovacs and E. F. Hartung (*Ibid.* 21:1022 (July) 1936),

from an analysis of antropometric and psychologic observations upon 100 females, 50 of whom had atrophic and 50 had hypertrophic arthritis. In this series the atrophic as compared with the hypertrophic patient is 20 pounds lighter in weight, has a shorter span length, a longer, narrower neck, a lesser thoracic anteroposterior diameter, chest and abdomen circumference. According to the Pignet index, the atrophic has a well-developed constitution in only 30 per cent., whereas 96 per cent. of the hypertrophics are so classified. No psychologic differences between the groups were established.

The rôle of *bacteria* as etiological factors has long enjoyed the attention of investigators. C. McEwen, R. C. Alexander and J. J. Bunim (*Ibid.* 21:453 (Feb.) 1936), in a study of blood cultures on 310 patients with various types of joint diseases and 149 controls, find that from 10 to 19 per cent. show the presence of green, hemolytic and indifferent streptococci and diphtheroid bacilli. However, these are not regarded as etiologically significant inasmuch as similar findings were obtained in diseases known to have other causes. These authors conclude that with the exception of the small group of patients with hemolytic streptococcal arthritis associated with frank septicemia, blood cultures are of no practical value in differentiating various varieties of arthritis.

In addition to those well-known instances in which more or less direct evidence indicates an etiological relationship of bacteria to active arthritis, several somewhat indirect lines of evidence have been advanced. The fact that the early and most prominent pathological change characterizing atrophic arthritis is proliferation and that the usual clinical picture shows inflammation, is cited as evidence of an infectious etiology.

M. H. Dawson and T. L. Tyson (*Ibid.* 21:575 (Mar.) 1936) cite the presence of nodules and agglutinins which they interpret as indicating that both rheumatic fever and atrophic arthritis have a common etiology and differ only because of age and host susceptibility.

C. McEwen, J. J. Bunim, R. C. Alexander (*Ibid.* 21:465 (Feb.) 1936), in a study of *immunologic tests* in several varieties of arthritis, conclude that gonococcus complement fixation reactions are positive in most cases of gonococcal arthritis; that 86 per cent. of atrophic arthritics show high agglutination titers for hemolytic streptococci; that anti-streptolysin titers are above normal in 66 per cent. of atrophics. The sera from patients with hypertrophic arthritis, gout, scurvy, and pyogenic arthritis failed to exhibit these properties. M. H. Dawson and M. Olmstead (*Proc. Soc. Exper. Biol. and Med.* 34:80 (Feb.) 1936) extended their earlier observations to show that the sera of artrophic arthritics agglutinate group A hemolytic streptococci in high dilution, but fail to agglutinate groups B, C, D, E, F and G in the same way. Among control sera, only those from patients with known severe hemolytic streptococcal infection exhibit to the same degree the property of agglutinating these organisms. Furthermore, sera from atrophic arthritics were found to contain precipitins for group specific substances obtained from organisms of groups A and B, but little of groups C to G. The reactions cited do not exactly parallel the clinical activity of the arthritic process. Further investigation is necessary to determine whether the frequent circumstantial evidence of the presence of hemolytic streptococci is of primary or of secondary importance in regard to etiology. In spite of the necessary limits of interpretation, these facts do reflect part of the dynamic pathology of the disease

insofar as they provide evidence of a deviation from the usual course of physiological processes and must be evaluated in any serious attempt to understand the nature of the origin of disease.

In the same category mention should be made of the presence in atrophic arthritis of an increased sedimentation rate and of a "shift to the left" of the polymorphonuclear cells.

M. H. Dawson and M. Olmstead (*Ibid.* 34:80 (Feb.) 1936) find that early cases of atrophic arthritis, *i. e.*, those seen within one year from the date of onset, exhibit high antistreptolysin titers, whereas in older cases they are normal.

Adding to the known list of *agents injurious to joints*, E. P. Jordan (*J. Lab. and Clin. Med.* 22:1 (Oct.) 1936) has produced synovial changes in rabbits simulating those found in rheumatoid disease by intraarticular injection of turpentine. L. J. A. Parr, of Sydney, Australia (Personal Communication), obtained evidence of the production of pathology of hypertrophic arthritis in rabbit joints, following intraarticular injection of streptococcal broth cultures. Although these changes were apparently induced by the bacteria, viable organisms were not recovered from these tissues. Control joints of the opposite leg were negative in all cases.

The possibility that *nutritional factors* may in some instances underly certain of the pathological features which may accelerate or pave the way for arthritis is indicated by observations of W. M. Gafafer (*Am. J. M. Sc.* 192:669 (Nov.) 1936) on the incidence of physical defects such as carious teeth, defective tonsils and adenoids among 30,000 white children ranging in age from 6 to 14 years, in relation to nutritional status. Of the boys, 6.5 per cent. showing physical defects had a poor nutritional

status, whereas only 3.8 per cent. of the nondefective presented evidence of a poor nutritional background. For girls the ratio was 10.2 and 5.4 per cent., respectively. The evidence is regarded as significant that minor infections and such physical defects as carious teeth, pyorrhea, and defective tonsils are correlated with nutritional impairment. Further suggestive data along this line is presented by E. C. Warner and F. G. Winterton (*Quart. J. Med.* 4:227 (July) 1935) from a study of the dietaries of juvenile patients with rheumatic disease, which indicates that the consumption of animal proteins and of dairy products of both rheumatic and control children of the social group wherein the disease is most common, is low and the consumption of concentrated carbohydrates is high. Prophylactic measures designed to correct some of the evident deficiencies with respect to vitamin A and D were inadequate to reduce the incidence of rheumatic attacks.

J. F. Rinehart (*Ann. Int. Med.* 9:586 (Nov.) 1935) records data which suggest that rheumatic fever may result from the combined influence of vitamin C deficiency and infection. Rinehart (*Ibid.* 9:671 (Dec.) 1935) has presented further evidence to suggest that subacute vitamin C deficiency may lead to the production of lesions in animals similar to those found in atrophic arthritis. A few patients responded favorably to the addition of liberal quantities of vitamin C to the diet. The observations, indicating a reciprocal relationship of seed and nutritional soil as a conditioning factor in the etiology of rheumatoid diseases, are in principle at least in line with much clinical suspicion. J. Sendroy, Jr., and M. P. Schultz (*J. Clin. Investig.* 15:369 (July) 1936), however, in comparing rheumatic fever subjects and controls, found little evidence, on the basis of vitamin C balance

studies, to support the view that rheumatic subjects suffer from deficiency of ascorbic acid. Furthermore, the latter investigators found that whereas ascorbic acid therapy decreased capillary permeability, it did not prevent the development of rheumatic manifestations. These findings show that whereas nutritional deficiency may play a part in leading to special tissue disorganization, the correction of single factors alone does not provide an adequate program to meet the complicated situation presented by the syndrome.

The importance of *age* as a factor influencing the type of arthritis has recently received considerable emphasis. W. Bauer and G. A. Bennett (*J. Bone and Joint Surg.* 18:1 (Jan.) 1936) have confirmed the incidence of hypertrophic lesions in the joints of older persons and their comparative absence in younger individuals. These authors regard hypertrophic arthritis as a degenerative disease only and consider that the wear and tear of increasing age and repeated traumata constitute the most important factors in production of joint lesions. The overgrowth of the hypertrophic joint is regarded as an expression of repair activity.

There are several factors which may conceivably accelerate the progress of degenerative changes in the body. Mechanically-induced microtraumata may play an important rôle in this connection, but this alone does not appear to be the only influence. The chemical wear and tear brought about as a consequence of systemic factors, including low-grade toxemias incident to focal infection or other factors, nutritional imbalances, and the sum total of those factors involved in the aging processes is to be emphasized.

It is evident in the light of these studies that the response of joints to many different sorts of influences may

lead to changes of arthritic nature and this fact appears to conform to clinical experience which indicates that not one but many factors must be taken into account.

**Differential Diagnosis.**— Proper diagnosis is prerequisite to the institution of adequate therapy. Unfortunately, the problem of diagnosis is sometimes confusing and often because of this no attempt is made to focus sharply enough to discern the differences which present. An extensive survey of features important in differential diagnosis was made at a meeting of the American Association for the Study and Control of Rheumatic Diseases (J. Lab. and Clin. Med. 22: 1 (Oct.) 1936). R. H. Boots (*Ibid.* 22: 14 (Oct.) 1936) points out that *atrophic arthritis* differs from *hypertrophic arthritis* in that the former shows positive agglutinins for hemolytic streptococci in more than 50 per cent. of cases; an increased sedimentation rate; and often a slight leukocytosis; whereas the latter exhibits slight if any changes in this direction. The former shows early evidence of osteoporosis, periarticular swelling and joint effusion, and, finally narrowing of the joint space, bone destruction, ankylosis, and marked muscular wasting; while the latter shows no osteoporosis, does show lipping at joint margins and, finally, osteophytes, without marked muscular wasting.

J. L. Miller (*Ibid.* 22: 19 (Oct.) 1936), differentiating *atrophic spondylitis* from *hypertrophic spondylitis*, points out the fact that the former begins in the small articulations of the spine as an inflammatory process, which also involves the spinal nerves. Coincident with these processes, osteoporosis of the vertebræ occurs. These changes are followed by ankylosis and ossification of the intervertebral ligaments, occasionally with extension of the spongiosa of the vertebræ through the discs. Infectious

factors appear to be etiologic. On the other hand, hypertrophic lesions in the spine begin with decreased resiliency and thinning of vertebral discs, followed by greater strains upon the intervertebral ligaments which enter the periosteum of the vertebræ adjacent to the vertebral rim. The resultant irritation of the periosteum leads to the formation of osteophytes along the course of attachment. Degenerative factors appear to be etiologic. Differentiation of these two types in late stages is easily made upon the basis of x-ray features, *viz.*, osteoporosis, round, smooth, bamboo-stick appearance of calcified intervertebral ligaments in the atrophic variety and irregular osteophyte formations, the lack of osteoporosis and in the hypertrophic type.

R. A. Kinsella (*Ibid.* 22: 26 (Oct.) 1936) points out the factors differentiating *rheumatic fever* from Still's disease, acute atrophic arthritis, arthritis incident to acute bacterial invasion about the joints, acute gout, and early phases of gonococcal rheumatism. The principal criteria for a diagnosis of rheumatic fever center around the fact that it is associated with cardiac lesions, while the other members lack this symptom. *Still's disease* is characterized by a more insidious onset, a persistence of joint involvement, a greater tendency toward an involvement of lymph nodes and spleen than occurs in rheumatic fever and is further distinguished by a lack of cardiac involvement. Similar considerations apply to the diagnosis of *acute atrophic arthritis* of the young adult. Severe *infections* may simulate rheumatic fever, but lack the periodicity of attack and the persistence of cardiac lesions. Early *gonococcal arthritis* may resemble rheumatic fever, but may be distinguished by the presence of associated genitourinary infection and freedom from heart disease. *Gout* and *acute stages of hypertrophic arthritis* occur in

later life and are not often confused with rheumatic fever.

W. C. Campbell (*Ibid.* 22:30 (Oct.) 1936) indicates that uncomplicated *traumatic arthritis* exists only as a definite entity in the young and is usually monoarticular. The pathologic picture is variable, but in the main presents that of localized hypertrophic arthritis arising as a result of constant irritation incidental to the functional activity of a more or less incongruous joint. There may be local osteoporosis with mottling at the end of the bone from a vasomotor influence. This is to be distinguished from the atrophy of disuse, which presents evidence of extension to the cortex. The chief diagnostic factor is the history of injury, followed shortly by the appearance of symptoms. Trauma may be a determining factor in the localization of other types of joint disease. The injured tissues constitute a locus minoris resistentiae, more easily subject to influence from noxious agencies. Mechanical injury to joints already affected by some form of arthritis may be more serious than that of a similar injury to a normal joint, and, furthermore, the sequelæ are often more disabling than the original injury.

C. H. Slocumb (*Ibid.* 22:56 (Oct.) 1936) regards *intramuscular fibrositis* as not likely to simulate arthritis, although *periarticular fibrositis* may often be mistaken for it. The final diagnosis depends upon the fact that fibrositis occurs without interference with the original integrity of the joint *per se*. Fibrositis is distinguished by clinical evidence that articular tenderness and marked muscular atrophy are both lacking. Stiffness is largely subjective; hydrops from synovial reaction is absent; ordinary motion is usually painless, and, indeed, mobility may be increased as a result of voluntary motion; remissions are frequent;

systemic manifestations are usually absent or minimal; and loss of weight is often slight in fibrositis. Periarticular fibrositis presents little if any x-ray evidence of intraarticular change. The sedimentation rate is slightly, if at all, accelerated and there is a lesser tendency to anemia. The systemic manifestations are, on the whole, distinctly less than in arthritis and this provides sufficient grounds for differentiation.

F. D. Dickson (*Ibid.* 22:35 (Oct.) 1936) points out the considerations required to differentiate *tuberculous arthritis* from other varieties. Tuberculous arthritis tends to be monoarticular and to occur in early life. The history usually reveals exposure to tuberculosis and an insidious onset. Pain develops relatively late in the course of the disease, but the changes are chronically progressive. The regional incidence of affection is indicated in a series of 158 cases in which involvement occurred in the spine in 62, in the hip in 41, in the knee in 25, in the ankle in 11, in the wrist in 10, in the sacroiliac in 6, in the shoulders in 2, in the elbow in 1. Constitutional symptoms are frequently absent. Limitation of motion is slight, swelling is boggy and unlike that of the effusions with much muscle atrophy which mark atrophic arthritis. The appearance of lesions may be similar to that of syphilitic synovitis. Late x-ray studies show thinning of cortex, destruction or thinning of cartilage, decalcification of bone ends, lack of new bone formation, presence of a focus of bone destruction in epiphysis, which tends to involve the neighboring joint. Multiple articular tuberculosis is rare and is distinguished from other forms in that it tends to be asymmetrical. Tuberculous arthritis of Poncet differs from atrophic arthritis only because of evidence of tubercular infection in the former.

Recalling the concept of Poncet regarding a tuberculous factor, W. S. C. Copeman (Reports Chronic Rheumatic Diseases No. 2, 1936) presents data which indicate that 30 to 40 per cent. of cases of atrophic arthritis show features which may be regarded as evidences of a low-grade tuberculous infection, including pyrexial onset with fatigue, increased sensitivity to tuberculin, periodicity of attack, familial incidence of tuberculosis, and occasional development of frankly tuberculous joints. On the basis of these findings, a consideration of tuberculous factors as etiological agents in atrophic arthritis is suggested.

The fact that *gout* occurs chiefly in males (98 per cent. of cases) and occurs most frequently after the age of forty years is reemphasized by P. S. Hench (J. Lab. and Clin. Med. 22:48 (Oct.) 1936). Gout may be distinguished from atrophic arthritis by the fact that the onset of pain is rapid and reaches a maximum in 2 days. Complete symptomatic remissions lasting for months often occur. As the disease progresses, the attacks become more frequent and the joint changes become chronically progressive. The swelling is often hot, bluish red, and is asymmetrical. Gouty arthritis is prone to be precipitated by dietary indiscretion, exposure, trauma, and occasionally develops during post-operative periods, during application of ketogenic diets, insulin and iron therapy. Coincident occurrence of nephritis, renal calculus, polycythemia and leukopenia are suggestive, and the appearance of uratic tophi is pathognomonic. Areas of bone erosion, if present, are more irregular in shape than the corresponding features in atrophic arthritis. Hyperuricemia is not a consistent feature but, when present, is highly significant.

It is pointed out by J. L. Warren (*Ibid.* 22:44 (Oct.) 1936) that *acute*

*gonococcal arthritis* can usually be easily recognized from a history of exposure followed by appearance of extremely severe articular or periarticular involvement. While positive cultures may be obtained in 80 per cent. of joint tissues when tested during early stages, later tests are often negative. Diffuse atrophy of the muscle and the tendon structures and marked bone destruction are prominent. There is usually evidence of extreme intoxication with prostration. Secondary bacterial invasion of the genitourinary tract may often constitute an important source of chronic focal infection.

Some of the conditions which occasionally may be mistaken for arthritic disorders are cited by W. J. Kerr (*Ibid.* 22:44 (Oct.) 1936) as follows: *Syphilis*: the history, presence of other syphilitic lesions, and serologic tests establish the diagnosis. The articular lesions include not only the Charcot type, which may present bizarre features of atrophic and hypertrophic character, but also less distinctive features, periostitis, fusiform swelling of fingers. *Hemophilia*, with hemarthrosis due to bleeding in the synovial membrane, may lead to progressive articular change simulating hypertrophic arthritis, but is easily distinguished by the history and delayed clotting time. *Scurvitic* changes in the joint are suggestive of atrophic arthritis, but the capillary fragility, the generalized tendency toward hemorrhage, along with graphic response to vitamin C, easily separates this entity. *Beriberi* of the *dry type*, showing pain and weakness in the extremities, with parasthesias, muscular tenderness, and of the *wet type*, with edema masking nutritional wasting, may simulate part of the symptoms evident in atrophic arthritis but the history of dietary deficiency and response to nutritional factors establish the diagnosis. *Rickets* in children may, because of

swelling in the ends of bones, grossly simulate in its early stages atrophic arthritis. However, irregularity of the epiphyseal line evident in roentgenograms, along with the history and general clinical picture, should leave little room for serious doubt as to diagnosis. *Raynaud's disease* and *scleroderma* are frequently associated in the late stages with bone changes similar to those seen in leprosy and with gross joint changes. These changes appear to follow an altered blood supply. *Leprosy* leads to marked alterations in the bones and joints, but the coincidence of other lesions of leprosy in other tissues usually establishes, by exclusion, the diagnosis. *Erythralgia* may be associated with joint pathology arising as a resultant of the vascular and nervous derangement. Fixation from disuse and contractures may eventually appear. *Peripheral neuritis*, occurring as a result of a variety of intoxications, may lead to painful joints resembling atrophic arthritis. Both *diabetes* and *primary anemia* may cause sensory symptoms of articular disease. *Periarthritis*, *Paget's disease*, *intermittent claudication*, may lead to sensory symptoms. The pain of *osteomyelitis*, *herpes zoster*, *von Recklinghausen's disease*, *psychogenic* and *referred visceral pain*, may mimic the pain of arthritis.

**X-ray Features.**—E. W. Spackman (Am. J. Roentgenol. 35:156 (Feb.) 1936) reports a statistical study of 1000 cases of *chronic arthritis*. The fact is emphasized that a clear cut diagnosis cannot be made upon the basis of x-ray studies alone. The following description of the early, middle, and late stages of atrophic and hypertrophic arthritis is presented:

*Stage I* of *atrophic arthritis* shows rarefaction of the trabeculated ends of bone with irregularity but preservation of the zone of calcification, slight haziness of joint space, along with widening,

then narrowing of joint space. *Stage II* shows atrophy of bone ends, including shaft, marked irregular contact of bones with islands of remaining cartilage, firm ankylosis, thickening of periarticular tissues, and calcium deposits around joint margins. *Stage III* shows generalized bone atrophy, partial disappearance of the zone of provisional calcification, enlarged punched-out areas, deformity due to softening and telescoping of bone, continuity of medullary bone and cortex, and generalized muscular atrophy.

*Stage I* of *hypertrophic arthritis* presents small osteophytes, narrowing joint space, altered alignment of bones, irregularity of articular surface with broadening, and secondary atrophy of honeycomb type. *Stage II* presents a picture of well formed spurs, obliteration of joint space, subluxation, thickening zone of calcification, saw-toothed articular surface with punched-out areas, increased circumference of articular surface with formation of Heberden's nodes, and advanced secondary atrophy. *Stage III* shows large irregular spur formation, gross irregularity and deformity secondary to erosion, subluxations, eburnation of bone, punched-out areas, increased articular area, advanced atrophy with occasional bending of bones.

An analysis is presented by G. D. Taylor, A. B. Ferguson, H. Kasabach and M. H. Dawson (Arch. Int. Med. 57:979 (May) 1936) of the x-ray features found in groups of cases which show typical clinical patterns corresponding to atrophic, hypertrophic, tuberculous, and gonococcal arthritis, Strumpel-Marie spondylitis and Still's disease. Little or no x-ray changes appear in the very early stages of these diseases, and no single pathognomonic features characterizes any one type, although clear cut patterns do characterize each variety. The same general features dominate the

picture of *atrophic arthritis*, *Strumpel-Marie spondylitis*, and *Still's disease*, viz., systemic decalcification, narrowing, and obliteration of joint space. In addition to these features, atrophic arthritis presents evidence of lipping in 77 per cent. of cases, atrophic bone destruction in 85 per cent., atrophy of soft tissues in 33 per cent., swelling in 41 per cent., and effusion in 88 per cent. Hypertrophic arthritis presents only a mild degree of systemic decalcification and this is commensurate with age. Lipping, with osteophyte formation, is present in 100 per cent., bone destruction in only 9 per cent., narrowing of joint space in 59 per cent., ankylosis in spine only, if at all, with soft tissue changes in less than 10 per cent. of the cases. Gout presents regional decalcification in 33 per cent., lipping and osteophytes with atrophic bone destruction in 85 per cent., narrowing joint space in 67 per cent., ankylosis in 17 per cent., atrophy of soft tissues in 17 per cent., swelling in 67 per cent., and effusion in 75 per cent. of the cases. Gonococcal arthritis presents regional and local decalcification in 36 and 64 per cent. respectively, lipping in 18 per cent., atrophic bone destruction in 18 per cent., and active destruction in 36 per cent., swelling in 27 per cent., and effusion in 64 per cent. of the cases. Tuberculous arthritis presents regional and local decalcification in 78 and 72 per cent., lipping in 34 per cent., active bone destruction in 84 per cent., narrowed joint space in 78 per cent., ankylosis in 9 per cent., soft tissue atrophy in 66 per cent., swelling in 70 per cent., and effusion in 72 per cent. of the cases. Information as to the duration of symptoms, the severity of the disease, and the mobility of the joints is required for adequate interpretation of x-ray changes.

**Dynamic Pathology.**—The changes in function which develop coincidentally

with the articular pathology are numerous. Measurable changes occur with significant frequency in the total, the nitrogen, the carbohydrate, the salt, the water and the lipoid metabolism. None of these is pathognomonic for any variety of the disease, but each is important as regards the individual problem confronting the patient who presents it. Furthermore, each system of the body is involved to a greater or lesser degree by the disease. The deviations which are reflected in the nervous system, respiratory and gastrointestinal systems are not peculiar to arthritis, but are none the less important. Some of the features which have received attention include the observation of E. F. Hartung, J. S. Davis, Jr., O. Steinbrocker and M. E. Straub (J. A. M. A. 100:1448 (Apr. 25) 1936), who summarize data collected on various components of the blood in atrophic and hypertrophic arthritis in a series of 100 atrophies, found that 96 showed abnormal neutrophil counts with an average of 29.6 per cent.; whereas, only 53 of 100 hypertrophies presented an abnormal count averaging 21.6 per cent. These differences were evident, although the total leukocyte counts were essentially similar in both groups. Serum calcium levels in corresponding groups fall within normal limits, although the statistical average for atrophies was 10.21 and for hypertrophies 9.98. Plasma cholesterol levels of 195 mg. per 100 c.c. for 33 normals, 175 for 33 atrophic, and 235 for 59 hypertrophies were found. The cholesterol esters made up similar proportions of the total in all instances. The total plasma protein in 16 severe atrophies averaged 7.35 per cent., with an average albumin globulin ratio of 0.9; a fibrinogen 0.63 per cent. Agglutinins for streptococcal strains AB<sub>13</sub>, NY<sub>5</sub>, C<sub>17</sub>, were found to be present in the sera of atrophic arthritides but not in normal



controls or in hypertrophics. Positive precipitin reactions also occurred with an extract containing type specific protein M. In the opinion of these investigators these findings lend support to the view that infectious factors play a dominant rôle in the etiology of atrophic arthritis and that degenerative processes dominate the background of hypertrophic arthritis.

From a study of the plasma proteins of 60 patients with arthritic diseases J. S. Davis, Jr. (J. Lab. and Clin. Med. 21:478 (Feb.) 1936), concludes that the globulin tends to rise in atrophic arthritis, the greatest change occurring in the englobulin fraction. There is little if any change in the plasma proteins in hypertrophic arthritis. The albumin tends to decrease in atrophic arthritis and the fibrinogen to increase. The albumin-globulin ratio is reduced in atrophic arthritis and not significantly changed in hypertrophic arthritis.

The increased *sedimentation rates* in *rheumatic fever* are attributed by A. F. Coburn and E. M. Kapp (J. Clin. Investigation 15:715 (Nov.) 1936) to increases in fibrinogen and globulin. Immunological tests for qualitative differences in plasma protein fractions of normal and rheumatic patients yielded negative results.

E. F. Hartung and O. Steinbrocker (Ann. Int. Med. 9:252 (Sept.) 1935) find in a study of *gastric acidity* in 70 patients with chronic arthritis that achlorhydria occurred in 21.6 per cent. of cases with rheumatoid arthritis and in 25.6 per cent. of cases with hypertrophic arthritis; hypochlorhydria was present in 17 per cent. of the former and in 3 per cent. of the latter. The incidence of reduced acidity among arthritics is distinctly greater than that in normal persons of the same age groups and is therefore regarded as an important fea-

ture of the disease though in no sense is this feature pathognomonic.

**Treatment.**—The principles of treatment are summarized by E. E. Irons (Ann. Int. Med. 9:1658 (June) 1936). While for purposes of classification studies of groups may be useful, for purposes of treatment the study of the individual patient is essential. General measures such as **rest**, **removal of infection** and provision of **optimal nutrition** in the provision of a well-balanced **diet**, including milk, eggs, meat, fruit and vegetables, affording ample supplies of protein and fat, are of the first importance. Drugs are to be regarded as accessory measures and not as means of affording adequate control alone.

L. T. Swaim (J. Lab. and Clin. Med. 21:532 (Feb.) 1936), evaluating the contribution of orthopedic care in arthritis, regards prevention of flexion deformity by **rest of the joint with casts and shells** as reasonably to be expected. The application should be followed by judicious use of the part. The straightening of recent contractions by casts is also practicable. Operative procedures, such as **synovectomy** to restore functional use, are also useful. **Arthroplasties** and **capsuloplasty** are more limited in application. General measures designed to **correct strain** upon joints are of wide utility.

J. S. Coulter (*Ibid.* 21:497 (Feb.) 1936) shows that the **physical therapy** measures most widely useful can be carried out in the home of the patient under appropriate direction. Exercise designed to restore tone of musculature and to correct postural or static defects, along with adequate **rest in bed**, should be carried out with adequate psychologic stimuli, such as may be provided by **occupational therapy**. The application of **heat** can be made with inexpensive appliances. **Massage** of the tissues provides a useful adjunct to other physical

measures which stimulate blood and lymph flow.

In a further observation on the use of **streptococcal bacterin** in *chronic rheumatoid arthritis* C. W. Wainwright (Ann. Int. Med. 9:245 (Sept.) 1935) notes that 79 of 87 cases of atrophic arthritis showed agglutinins for hemolytic streptococci in sera; 75 of 78 cases showed skin reactions to one or more strains of streptococci; 88 per cent. showed maximal reactions to hemolytic strains; whereas, 8 per cent. showed reaction to viridans strains; 4 per cent. showed no skin reaction; 30 of 45 cases exhibited improvement upon the intravenous use of vaccines from strains to which patients were most sensitive.

P. S. Hench (J. Lab. Clin. Med. 21: 524 (Feb.) 1936) summarizes his own experience coupled with published data and concludes that a patient with early *gonococcal arthritis* has an 80 per cent. chance of being benefited by **fever therapy**. Similar therapy applied to an acute atrophic provides only a 10 per cent. chance, whereas a chronic atrophic or hypertrophic arthritic could expect only a 5 per cent. chance of being materially improved. Data on other groups are too few for adequate evaluation.

T. G. Schnabel and F. Fetter (Ann. Int. Med. 9:398 (Oct.) 1935) note that **fever therapy** induced by hyperthermia resulted in improvement in 12 cases of *chorea* and 18 cases of *gonorrheal arthritis*, save in one, who died as a result of a breakdown of her temperature control mechanism.

R. L. Cecil, C. Friess, E. E. Nicholls, W. K. Stratman-Thomas (J. A. M. A. 105:1161 (Oct. 12) 1935) cite experiences with **malarial therapy** in 12 cases of long-standing *atrophic arthritis* and 1 case of 4 months duration. Immediate symptomatic improvement was noted in all cases. Except for the one early case, relapses occurred, in 8 instances to the

original states; in 4 cases relative improvement was maintained.

The use of a **leukocytic cream** in 10 cases of *atrophic arthritis* is reported by E. E. Hartung (J. Lab. and Clin. Med. 21:536 (Feb.) 1936). The cream was prepared from blood taken from healthy subjects. From 3 to 6 c.c. of the concentrate was administered intragluteally 3 to 7 times per week for 3 weeks to 9 months. No case was cured, although 6 showed distinct symptomatic and constitutional improvement. However, no significant changes occurred in the blood counts or sedimentation rates.

Recent studies on the use of **cinchophen** in 2500 cases are reported by R. G. Snyder, C. H. Traeger, C. H. Zoll, L. C. Kelly and F. J. Lust (*Ibid.* 21:541 (Feb.) 1936). At the beginning of its use patients given doses of 7½ grains (0.5 Gm.) 3 times per day are seen at least 3 times per week, in order to detect evidence of gastric irritation, nausea or itching. The toxic effects attributed to the drug are regarded as due to idiosyncrasy and these authors believe that its use is reasonably safe when used judiciously.

B. L. Wyatt, R. A. Hicks and H. E. Thompson (Ann. Int. Med. 10:1 (Oct.) 1936) contrasted the progress of patients upon doses of **vitamin D** with that experienced for 6 months under a general regimen. In 8 of 40 cases with atrophic arthritis improvement resulted while 8 others had to abandon treatment because of unfavorable reactions. The remainder presented no contrast. Laboratory tests revealed no significant changes in metabolism.

The possible production of acute leukemia through the use of **gold salts** in the treatment of arthritis has been pointed out by R. Boulin, F. Cpste, P. Uhry and J. Antonelli (Paris Letter, J. A. M. A. 107:223 (July 18) 1936).

In this respect gold salts should be used with the same caution as x-rays, radioactive agents, benzene and tar preparations.

**Summary.**—It is apparent that recent work in the field of rheumatoid diseases requires material expansion of concepts regarding the etiology and nature of them. With respect to treatment, newer work, while incidentally increasing the number of procedures available, serves chiefly to emphasize the practical importance of a coördinated therapeutic program which recognizes the fact that

the chronic arthritic individual suffers from disability arising from disturbances in many systems of his body. It is increasingly evident that such broadly active measures as **rest**, provision of **optimal nutrition**, **removal of infection**, correction of mechanical or structural handicaps by **orthopedic** or **physical therapy**, **replacement or corrective agents** for metabolic defects, and **psychic adjustment** constitute, in broad outline, the formulations of rational therapy in this group of chronic diseases.

## CARDIOVASCULAR SYSTEM

Edited by WILLIAM D. STROUD, B.S., M.D.

### CARDIOVASCULAR CONDITIONS IN GENERAL

By ALBERT W. BROMER, A.B., M.D.

**BLOOD-PRESSURE. — *Diagnosis.***—*Cold Pressor Test.*—A simple test to measure a generalized vasomotor tonus, in which ice water is used as a stimulus, has been devised by E. A. Hines, Jr., and G. E. Brown (Am. Heart J. 11:1 (Jan.) 1936). After determining the basal level of the blood-pressure, with the patient at rest in a supine position in a quiet room, the cuff of the sphygmomanometer is placed on one arm of the subject and the opposite hand is placed in ice water (4°C.) to a point just above the wrist. Readings of the blood-pressure are taken at the end of 30 seconds and again at the end of 60 seconds, the maximal reading representing the index of the response. The hand is then removed from the ice water, and readings are taken every 2 minutes until the blood-pressure returns to its previous basal level. The maximal response usually occurs within 30 seconds. The blood-pressure of patients with normal levels returns to the basal level

within 2 minutes. In the presence of established hypertension, there is often delay in return to the previous level. Individuals vary in their sensitivity to ice water; for a few, the time of immersion is limited by the pain caused by the cold. However, there is no relationship between the degree of sensitivity and the response of the blood-pressure.

Two values seem of significance in the cold pressor reaction: (1) the increase in the blood-pressure from basal to maximal points, termed the "response or range"; and (2) the maximal values obtained in the systolic and diastolic pressures, termed the "ceiling" for the cold test stimulus. This ceiling is held for a variable time after application of the test. The most probable explanation of the rise of blood-pressure in the test is that the response is a widespread vasopressor reaction initiated through a neurogenic reflex arc. During the test there is no significant change in cardiac rate or in cardiac output.

In repeated tests on 25 individuals with normal blood-pressures, and on 20 with essential hypertension, after intervals of from 3 months to 3 years, there was an average variation in range of response of only 10 per cent. In no case did an individual with a range of less than 18 mm. Hg. in systolic and diastolic pressure give a subsequent reaction in the abnormal range, nor did a subject who revealed an abnormal range give a normal reaction. Several subjects with reactions in the maximal range of normal on repeated tests gave occasional reactions in the minimal range of the abnormal. In the entire group with normal levels of blood-pressure, there was found a definite increase in the reaction in the later decades of life, which may be interpreted as indicating that an abnormal hypertonicity of the vasomotor system may increase in intensity with age.

In a study of 571 subjects over a period of 3 years, 3 groups were recognized on the basis of response. "*Normal reactors*" (288 subjects) included normal persons and subjects suffering from a variety of diseases not associated with hypertension. In 96 per cent. of this group the rise in systolic and diastolic pressure was less than 15 mm. Hg., the mean increase being 11.4 mm. Hg. for the systolic and 10.6 mm. for the diastolic pressure. The second group, "*normal hyperreactors*," comprised 90 subjects of both sexes, from 4 to 75 years of age, with normal basal levels, who reacted excessively to the tests. The mean rise in blood-pressure was 29.4 mm. Hg. for the systolic and 24.5 mm. for the diastolic pressure. This group is of great significance, the question arising as to whether or not the subjects represent potential hypertension. Careful investigation disclosed that 78 of the 90 subjects had a positive family history of hypertensive cardiovascular disease. The authors hold to the belief

that essential hypertension eventually will develop in many individuals in this group. The third group, comprising 193 subjects with *essential hypertension*, varying in age from 24 to 64 years, was further divided into the *organic* type and *preorganic* type of hypertension, on the basis of the presence or absence of changes in retinal arterioles. The mean rise in the blood-pressure in the organic group was 47.2 mm. Hg. for the systolic and 34.3 mm. for the diastolic; in the preorganic group, the mean rise was 34.4 mm. for the systolic and 25.4 mm. for the diastolic pressure. The low and high values in the entire group were from 22 to 120 mm. Hg. for the systolic and from 20 to 70 mm. for the diastolic pressure. In both groups there was some delay in the return of the blood-pressure to the previous basal level: 97 per cent. of the organic group and all in the preorganic group had abnormal reactions in range; all of the subjects in both groups had abnormal ceiling values.

This study has demonstrated the following: (1) The response in blood pressure to a standard stimulation (cold) is fairly constant for the normal individual; (2) a few "normal hyperreactors" have been observed sufficiently long for essential hypertension to have developed; (3) persistent abnormal pressor responses have not been found in disease states other than essential hypertension. If the maximal or ceiling level exceeds 145 mm. Hg. for the systolic and 95 mm. for the diastolic pressure, a hyperreactive response to the test will be found in 97 per cent., while a ceiling value of 100 mm. or more for the diastolic pressure shows a hyperreactive response in 100 per cent. of cases. The pressor responses in vasospastic disorders, Raynaud's disease, and neurocirculatory asthenia are inclined to fall in the upper range for normal subjects.

In hyperthyroidism and neurocirculatory asthenia, there is an abnormal response in the systolic pressure only. The conclusion is drawn that the abnormality of essential hypertension is an excessive response in the blood-pressure to intrinsic and extrinsic stimulation, hereditary in character, appearing early in life and remaining during life. When the blood-pressure is elevated and clinical degrees of hypertension exist, the reactions then increase with increasing severity of the hypertension. This hyperreactive vasomotor mechanism may be an important factor in the production of arteriolar hypertrophy and in the subsequent development of the organic stages of the disease.

*Variation of Readings in the Two Arms.*—On the basis of 12,384 blood-pressure readings (*i. e.*, 6192 examinations) on a group of 516 patients during a period of 6 years in general practice, R. Southby (M. J. Australia 2:569 (Oct. 26) 1935) calls attention to the frequent occurrence of differences in the readings on the two arms. With the patient completely relaxed in the recumbent position, with arms outstretched at the level of the heart, the armlet was applied just below the axillary fold. The bag was inflated for some time after no sounds were heard, and the pressure was then gradually released. The systolic pressure was read at the moment when the first clicking sound came through (the commencement of the first phase), and the diastolic pressure at the transition from the third to the fourth phase (when the thudding sounds change to a few dull muffled sounds which precede absolute silence).

Analysis of the readings recorded on the first examination of each patient showed an appreciable difference in the readings on the two arms in all age groups. Figures for the right arm for all ages and for both sexes were higher

than those accepted as normal by 8 insurance companies, whereas the figures for the left arm approached the standards more closely, except in females over 50 years of age. Blood-pressure readings increase with age more rapidly in females. The difference between the two arms was much greater in some individuals, and was usually greater the higher the systolic reading in the right arm. Very rarely did the readings in the two arms correspond exactly, and only occasionally was the reading higher in the left arm than in the right.

A survey of all the deaths known to have occurred during the study, grouped according to whether the individual exhibited large or small differences in the pressure of the two arms, showed: (1) Sex distribution was approximately the same, each group showing a slight preponderance of females; (2) it was exceptional to find great urinary changes in cases with small-differences (less than 20 mm. Hg. systolic or 10 mm. diastolic) between the two pressures, but with large-differences, it was unusual to find the urine normal; (3) the most frequent causes of death in the small-difference group (constituting 40 per cent. of this series) were malignant disease, mild carditis with cardiac failure, and pulmonary tuberculosis; in the large-difference group, cerebral vascular lesions, angina pectoris, or uremia; (4) the number of deaths in the large-difference group was two and one-half that in the small-difference group. The prognostic importance of a raised diastolic pressure is demonstrated by the fact that only 4 of 19 patients with a diastolic pressure of 100 mm. survived the 6-year period of study and maintained good health in addition.

A simple explanation of the variation in pressure between the two arms, based on personal hydrostatic experiments, is suggested by Southby. Since the innom-

inate artery, from which arises the right subclavian, is more in the direct line of the stream of blood in its upward thrust from the ascending aorta than is the left subclavian, which arises further along the arch of the aorta and in a direction almost at right angles to the flow, it would appear reasonable that the pressure in the right subclavian (and consequently in the axillary and brachial arteries) is ordinarily greater than that in the left subclavian, axillary, and brachial arteries.

In any clinical examination, the blood-pressure readings should be taken on both arms and considered in conjunction with the urinary findings before the state of the cardiovascular system is assessed.

**HYPERTENSION.—*Etiology.***—*Carotid Sinus Reflex.*—The observation that a state of elevated blood-pressure develops in animals after denervation of the carotid sinus and aortic arch has suggested that certain forms of hypertension in man might similarly be due to a failure of the depressor mechanism. The evidence has been summarized by G. D. Gammon (J. Clin. Investigation 15:153 (Mar.) 1936) as follows: direct stimulation of the carotid sinus endings in hypertensive patients by digital pressure over the walls of the sinus causes a marked fall in blood-pressure; however, alteration of pressure within the carotid sinus by digital compression and release of the common carotid artery below the sinus produces only minimal or negligible changes in blood-pressure or heart rate. The conclusion has therefore been drawn that in hypertension there exists a certain degree of insensitiveness of the carotid sinus endings to their physiological stimulus, namely, changes in intravascular pressure within the sinus. Furthermore, the suggestion has been made that in these patients this defect is, in part at least, responsible

for the development of the elevation of blood-pressure.

In a study of 31 patients with hypertension of either the essential type or that associated with arteriosclerosis, the carotid sinus test was performed by Gammon, as follow: "With the individual prone, the carotid sinus is compressed against the transverse processes of the vertebrae for a period of 30 to 60 seconds. The common carotid artery is compressed as low in the neck as is possible, attempting to avoid traction on the sinus. The carotid artery was obstructed for periods up to 2 minutes. Control observations were made by pressure on an indifferent part of the neck. Simultaneous determinations of blood-pressure and pulse rate were made before, during, and after these procedures. . . . Bilateral compression was never employed." The fall in blood pressure and heart rate was readily obtained by pressure over the sinus. The average fall was  $42\frac{1}{4}$  mm. Hg. on stimulation of the left sinus, and  $43\frac{1}{2}$  mm. Hg. on stimulation of the right. The fall in pulse rate was 16 per minute with a range of 0 to 42. No correlation was noted between the fall in blood pressure and the change in pulse rate; in many instances, maximum change in blood pressure was accompanied by little or no alteration in pulse rate. The fact that a fall in blood-pressure is obtainable in hypertensive patients on sinus stimulation demonstrates that the depressor arc in them is capable of functioning in all its parts, including the efferent motor nerves and the muscle of the vessel wall. Responses induced by occlusion and release of the common carotid arteries indicate that the carotid sinus nerve endings are sensitive to changes in intravascular pressure, contrary to the observation of others. The only way in which the hypertensive differs from

the normal is in a somewhat exaggerated degree of reaction.

The interpretation of the results of this study, *i. e.*, that the carotid sinus nerves are functioning normally in hypertensive patients of the type examined, taken together with other recent observations in such cases, supply some suggestive implications as to the nature of the process whereby hypertension is developed. Interruption of the nerve supply of large vascular areas in persons with high blood-pressure will lower the blood-pressure to normal levels. For example, the fall in blood-pressure which occurs in these patients after the induction of spinal anesthesia is greater than that obtained in normal persons. Furthermore, it has been claimed that surgical denervation of a considerable vascular area will result in a persistent drop in the blood-pressure, though further long-time observations on the point seem desirable. If, then, denervation of blood vessels lowers the blood-pressure of hypertensive patients to normal levels, and if the carotid sinus mechanism is functioning normally, the suggestion arises that the *modus operandi* of human hypertension, whatever the etiology, should be sought for either in some part of the depressor reflex arc other than the sensory discharge of the carotid sinus, or in an abnormal reaction of the vessels to the tonic vasoconstrictor impulses.

In a study of the anatomy of the carotid sinus region of the dog, C. F. Code, W. T. Dingle and V. H. K. Moorhouse (Am. J. Physiol. 115:249 (Apr.) 1936) found that the carotid sinus has 3 sources of nerve supply: a branch from the posterior division of the glossopharyngeal nerve, a branch from the superior cervical ganglion, and a small nerve which accompanies the internal carotid artery. By electrical stimulation, it was shown that (1) the nerve accompanying

the internal carotid artery is not concerned in the carotid sinus reflex, and (2) that the sinus nerve (from the glossopharyngeal nerve) is of greater importance than the sympathetic nerve. On the basis of acute and survival denervation experiments, it is concluded that in the dog the cardiovascular components of the sinus reflex are conducted solely through the sinus nerve. These experiments lend support to the view that the carotid sinus operates entirely through a depressor mechanism.

According to G. W. Pickering, M. Kissin and P. Rothschild (Clin. Sc. 2:193 (May) 1936), the features presented by patients suffering from the common forms of persistent hypertension differ so markedly from those exhibited by the animal with hypertension produced by denervation of the carotid sinus and arch of the aorta that an essentially different origin of human and experimental hypertension is suggested. Tachycardia is invariable in the experimental hypertension and exceptional in human hypertension; compression of the carotid artery below the sinus gives no response in the animal and a definite response in man; sensory stimuli produce a fall in blood-pressure in the animal and a rise in man; in sleep, the blood-pressure falls to normal in the animal and remains elevated in man; and characteristic histological changes in the arterioles are absent in the experimental and usually present in the human form. It is not to be denied that there may be examples of hypertension in man which are similar in origin to the experimental form; however, such cases must be uncommon and the authors are not satisfied that the evidence for their existence is adequate.

The function of the carotid sinus mechanism was tested in 4 groups of human subjects: (1) Young adults with

normal blood-pressure, (2) subjects with normal blood-pressure, (3) patients with chronic nephritis and hypertension, (4) patients with essential hypertension. The differences in the response to carotid sinus compression shown by the various groups seemed to be entirely unaccounted for by differences in the initial levels of blood-pressure and by differences in the degree of sclerosis of the large arteries. Digital obliteration of one carotid artery below the sinus produced, in all subjects with normal and high blood-pressure, rises of blood-pressure and pulse rate that were greater than those produced by control pressures on the neck and femoral artery.

*Peripheral Resistance.*—From the physiological point of view elevation of blood-pressure may be due to an increase in cardiac output, in the volume or viscosity of the blood, or in the resistance of the peripheral vessels. Since cardiac output is not increased in hypertension, and the viscosity and volume of the circulatory blood have been shown to be normal, there remains only the increased resistance in the peripheral circulation, which feature has recently been studied by M. Prinzmetal and C. Wilson (J. Clin. Investigation 15.63 (Jan.) 1936). In their investigation, the following questions received attention: (1) Is the increased peripheral resistance generalized throughout the systemic circulation or confined to the splanchnic area? (2) To what extent are the vessels responsible for the increased peripheral resistance capable of dilatation? (3) what part is played by the vasomotor nerves in the maintenance of the increased peripheral resistance; *i. e.*, if arterial hypertonus is present, can it be attributed to an increase in sympathetic vasoconstrictor impulses?

Determinations of resting blood flow in the arm (using the arm plethysmograph as described by Lewis and Grant)

in various types of hypertension (benign, malignant, and secondary) gave an average value no greater than that obtained from subjects with normal blood-pressure, which fact indicates that increased vascular resistance in the different types of hypertension is not confined to the splanchnic area, but is generalized throughout the systemic circulation. Patients with hypertension showed an increase in blood flow in response to heat and reactive hyperemia equal in degree to that produced in normal individuals, showing that the blood vessels in hypertension are capable of considerable dilatation and indicating that the increased peripheral resistance is due to hypertonus and not to organic changes in the vessel walls. Sympathetic vasodilatation produced by the "heat test" produced no greater increase in blood flow in subjects with high blood pressure than in normal individuals, suggesting that the vascular hypertonus is not vasomotor in origin.

Patients with coarctation of the aorta, on the other hand, showed a greater increase in blood flow in the arm in response to the heat test than controls or patients with generalized hypertension. This demonstrates that vasoconstriction of sympathetic origin is present in the upper extremities in coarctation of the aorta, and affords confirmatory indirect evidence that the hypertonus in generalized hypertension is not of vasomotor origin. Sympathetic vasoconstriction in the upper extremities in coarctation of the aorta may be regarded as a compensatory mechanism which maintains the normal distribution of blood throughout the body.

Novocaine anesthetization of the vasomotor nerves to the arm produced the same increase in blood flow in normal subjects and patients with hypertension, proving that the vascular hypertonus is independent of the vasomotor nerves,



and that this hypertonus must therefore be regarded as intrinsic spasm of the blood vessels themselves. Acute exacerbation of hypertension with change from the benign to the malignant type was observed in one case. Such exacerbation is apparently not due to increased vasomotor activity, but must be attributed to an increase in the intrinsic vascular hypertonus.

These conclusions apply to all types of hypertension studied, *viz.*, benign hypertension, malignant hypertension, and "renal" hypertension associated with acute and chronic glomerulonephritis and chronic pyelonephritis; hence, there is no physiological evidence for the separation into "organic" and "functional" types or for the assumption that renal hypertension is due to vasomotor hypertonus. It has been shown in both normal subjects and patients with hypertension that there is vasoconstrictor and vasodilatator innervation to the blood vessels of the arm. In this region greater variations in blood flow are produced by vasodilatator than by vasoconstrictor impulses. In the types of hypertension studied, it appears therefore that normal vasomotor activity is superimposed on the intrinsic vascular hypertonus.

Theoretically, some fall in blood-pressure may follow sympathectomy in patients with hypertension, since the normal vasoconstrictor tone is thereby abolished; but the *intrinsic vascular spasm* responsible for the hypertension would be expected to persist after the vasomotor nerves are cut.

**CORONARY ARTERY DISEASE.—Nervous Control of Coronary Circulation.**—Study of the nervous control of the coronary circulation of the dog by C. W. Greene (South. M. J. 29:478 (May) 1936) showed these blood vessels to be richly supplied with efferent neurons of both dilator and con-

strictor type. In the dog, the efferent dilator nerves from the central nervous system and spinal cord cover a wide spread in the sympathetic ganglionic chain, as between the superior cervical ganglion and at least the sixth dorsal ganglion. The dilator neurons are greater in mass effect, more definite in physiological control, and must obviously serve the primary function of increasing the coronary flow during augmented myocardial work. Coronary constrictor mechanisms, on the other hand, are more limited, the reaction is less voluminous, but in extreme development this portion of the cardiac mechanism may play an important part in producing attacks of functional angina.

The author stresses a new concept that these two great coronary nerve mechanisms are delicately controlled by very definite and specific reflex nervous mechanisms in adaptation to every delicate changing activity of the whole body. These reflexes are primarily coronary dilator in type; nevertheless, there may occur associated reflex coronary constrictions. In pathology of the myocardium, and especially of the coronary vessels, structural changes inevitably reduce physiological resilience and delicacy of adaptive response. Under conditions in which the normal animal reacts by increases in the coronary circulation corresponding to the increase in myocardial work, the pathological heart cannot give the corresponding dilatations of the coronary arterial system. Hence, there is failure of adequate coronary blood flow, and cardiac asphyxiation follows. Oxygen want is induced with the resulting spasms of pain. Of the two processes which can induce anginal attacks, the over-functional activity of the reflex coronary constrictor mechanisms seems to be of lesser significance than the blocking of functional dilatations by pathology of the vessel walls.

**Treatment.**—*Undernutrition.*—The effect of a low calorie diet (800 calories divided into 80 grams of carbohydrate, 50 grams of protein and 30 grams of fat) on the basal metabolism of 28 patients with coronary thrombosis and 14 with angina pectoris, whose control basal metabolic rates were within normal limits, has been studied by A. M. Master, H. L. Jaffe and S. Dack (J. Clin. Investigation 15: 353 (July) 1936). Fluids were restricted to 1200–1500 c.c., unless heart failure was present; and the diet was maintained beyond the acute phase of the thrombosis, usually 3 months, and then gradually increased to 2000 or more calories. After any of these periods, the diet was often again reduced to 800 calories for comparison. In 31 patients (74 per cent.) a successful drop of 15 to 35 per cent. in metabolism was obtained; in 6 it fell only 10 to 14 per cent., and in 5, less than 10 per cent. Two to 4 weeks were necessary for this drop to occur, and a similar period was needed for its return to normal following resumption of a regular diet. Therefore, despite the marked change in diet, the metabolism of the body was determined for several weeks by the previous state of nutrition.

With the occurrence of considerable loss of weight, the basal metabolic rate did not adequately reflect the actual drop in metabolism because of the changes in body surface, but generally a change in caloric intake eventually was associated with a distinctive change in rate. After a period of undernutrition, a subsequent period produced a more rapid and profound drop in basal rate. The loss of weight necessary to attain a significant fall in metabolism averaged 6 per cent. of the initial body weight. As a rule, only 1200 to 1500 calories were required to maintain weight when the patient was ambulatory. Several factors, such as insufficient loss of

weight, cardiac failure, infection of the upper respiratory tract and repeated anginal attacks, tended to prevent a significant fall in basal metabolism on this diet. No ill effects resulted from the prolonged undernutrition of from 3 to 12 months duration; the blood cholesterol, sugar and protein values were unaffected. Graduated increases in diet to 1200, 1500 and 2000 calories often resulted in corresponding rises in basal metabolism. The drop in metabolism was not associated with any evidence of hypothyroidism, such as myxedema, diminished blood velocity, and hypercholesterolemia; vital capacity was not affected. In general, this regimen affected the cardiovascular system favorably, resulting in slowing of the pulse rate, decrease in blood-pressure and pulse-pressure, and diminution of the cardiac output and work of the heart. It is concluded that the marked improvement in many of the most seriously ill patients, following resumption of a diet sufficient to maintain weight, indicates that undernutrition for a period of months may improve the condition of the patient to such an extent that radical measures, such as total thyroidectomy, will be unnecessary.

#### **CORONARY THROMBOSIS.**—

**Etiology.**—S. B. B. Campbell (Brit. M. J. 1: 781 (Apr. 18) 1936) points out an association between infection and the great increase in coronary thrombosis. *Infections of the gall-bladder* are those most commonly associated with this cardiac lesion. Various authors have claimed a cause and effect relationship between cholecystitis and coronary thrombosis. The difficulties in diagnosis are due to the fact that varying degrees of anginal pain can be simulated by gall-stone colic or the pain of cholecystitis. In gall-bladder conditions the pain may be referred to the precordium and left arm, while a right-sided dis-

tribution of pain may be found in coronary thrombosis. A previous history of abdominal symptoms, such as food intolerance, flatulence, and vomiting, is in favor of a gall-bladder lesion. Women are more prone to gall-bladder disease; also the age of the patient is important. Rigidity of the right rectus muscle and jaundice are practically diagnostic of cholecystitis.

The occurrence of temporary and sometimes permanent myocardial changes as sequels to *influenza* is well known. Many hypertensive patients have been active and fit for work until they become victims of this common infection. Infection is generally thought of in cases of phlebitis. Several cases that illustrate the association of coronary thrombosis with phlebitis and other forms of thrombosis have been observed. Some patients with coronary thrombosis gave a history of previous infection, such as *pneumonia*, *carbuncle*, *cystitis* or *pyelitis*. Cardiovascular *syphilis* complicated by the onset of coronary thrombosis is rare but does occur, as demonstrated in 2 patients who did well on antisiphilitic treatment after such diagnosis. Though the frequency with which coronary thrombosis and *diabetes* are associated is attributed to degenerative vascular changes, it should be borne in mind that acute and chronic infections are frequent in diabetes, and that coronary thrombosis occurs twice as frequently in diabetic as in nondiabetic patients. It is difficult to prove that these infections are the determining cause of the cardiac lesion; however, everything possible should be done to eliminate any focal infection with the hope of averting a cardiac tragedy.

**Prognosis.**—In a group of 243 patients with coronary thrombosis treated by A. M. Master, H. L. Jaffe and S. Dack (*Am. Heart J.* 12: 549 (Nov.) 1936) with the low calorie diet and pro-

longed rest in bed, the mortality rate in 267 attacks was 16.5 per cent.; in first attacks only 8 per cent. The incidence among men and women was in the ratio of 3 to 1. Coronary thrombosis occurs not infrequently in the fourth and fifth decades, and in these the prognosis is better than in the older age groups. The average age in this series was 54 years. Hypertension, which preceded the attack in 66 per cent. of cases, did not influence the prognosis. Hypertension or diabetes is usually present when coronary thrombosis occurs in women. Infarction of the anterior and posterior surface of the left ventricle occurred with equal frequency, with no difference in prognosis. Some cases are inevitably fatal because of the size of one or several simultaneous infarctions or because of the severe degree of involvement of all the coronary vessels. In this series of cases it appeared that in the main the prognosis of an attack is hopeful and that death in the first attack is infrequent.

**Treatment.**—Master, Jaffe and Dack (*Ibid.*) employed the following treatment: As soon as the diagnosis of acute coronary thrombosis was made or suspected, the patient was put to bed; **absolute rest and quiet** were enjoined. If pain was very severe, as much as  $\frac{3}{4}$  grain (0.058 Gm.) of **morphine** was administered within 12 hours without hesitancy. Morphine not only relieves pain but also lightens the work of the heart by slowing the rate and lowering the basal metabolism, diminishes respiratory effort, and tends to prevent paroxysmal cardiac dyspnea.

During the first few days very **little food** was given, especially to the very sick patients. **Fluids** were limited to 1000 to 1200 c.c. unless there was profuse perspiration. In the presence of *nausea and vomiting*, food was **withheld** and small quantities of **cracked**

## 800 CALORIE DIET

*Breakfast*

100 gm. 12 per cent fruit  
 10 gm. cereal  
 200 c.c. skimmed milk  
 1 egg  
 15 gm. bread

*Dinner*

60 gm. meat  
 100 gm. 3 per cent vegetable  
 100 gm. 12 per cent fruit  
 15 gm. bread  
 200 c.c. skimmed milk

*Supper*

1 egg  
 100 gm. 3 per cent vegetable  
 100 gm. 12 per cent fruit  
 15 gm. bread  
 200 c.c. skimmed milk

*Sample Menu*

$\frac{1}{2}$  medium orange  
 2 tablespoons cooked cereal  
 1 cup  
 1 egg  
 $\frac{1}{2}$  slice

2 ounces meat  
 $\frac{1}{2}$  cup spinach  
 3 plums  
 $\frac{1}{2}$  slice  
 1 cup

1 egg  
 $\frac{1}{2}$  cup canned string beans  
 1 medium peach  
 $\frac{1}{2}$  slice  
 1 cup

ice and charged water were given. With clinical improvement, the diet was slowly increased so that in from 5 to 7 days 750 to 850 calories were being given. The 800 calorie diet was maintained for at least 3 to 6 weeks, and frequently for much longer periods. Endeavor was made to satisfy the individual's tastes whenever possible. In only a minority of instances was there complaint of hunger, which usually could be allayed by a small evening portion or the addition of noncaloric candy, etc.; increasing the bulk of the food sometimes sufficed.

Digitalis, nitroglycerin, amyl nitrite, adrenalin and ephedrine were considered *contraindicated*. *Digitalis* is believed to increase precordial pain, and experimentally it has been found that dogs in which myocardial infarction had been produced were more susceptible to fatal digitalis poisoning. By lowering diastolic pressure in dogs, *nitroglycerin* has been found to increase the size of a myocardial infarct; also it increases the work of the heart. *Adrenalin* has been shown to produce pain in patients with an anginal syndrome; it also increases the work of the heart.

With *congestive failure*, fluid and salt were limited; digitalis was not prescribed, but injections of *mercupurin* were used when necessary. Cardiac arrhythmias developing during an attack were transitory in most cases, and required no specific treatment. No *cathartics* or enemas were given during the first 3 to 5 days. On the low diet prescribed, distention occurred rarely. **Oxygen therapy** was employed only in cases with cardiac failure or pulmonary complications, particularly in cases with severe dyspnea and cyanosis. Often it relieves pain, dyspnea and cyanosis; however, occasionally a patient was quite uncomfortable in the oxygen tent in spite of proper air conditioning and oxygen supply. The patient was kept in bed from 4 to 10 weeks, the average being 5½ weeks. He was then permitted gradually to get out into a chair, and usually by the seventh or eighth week he was able to walk.

During the two periods, 1930 to 1932 and 1933 to June, 1934, the *mortality rate* of ward patients at the Mount Sinai Hospital, New York, was 39.7 per cent. and 40.5 per cent., respectively, whereas since June, 1934, under the low calorie

TABLE I  
*Comparison of Methods of Treatment of Coronary Artery Thrombosis*

| Year     | Attacks | Deaths | Mortality Rate (%) | Mortality Exclusive 1st 24 Hr. (%) | Mortality 1st Attack (%) |
|----------|---------|--------|--------------------|------------------------------------|--------------------------|
| 1930-32* | 131     | 52     | 39.7               | 33.6                               | 36                       |
| 1933-34† | 111     | 45     | 40.5               | 33.0                               | 37                       |
| 1934-36‡ | 145     | 30     | 20.7               | 16.0                               | 10                       |

\*Regular diet. Digitalis and nitroglycerin.

†Regular diet only. (1933 to May, 1934)

‡Undernutrition only. (May, 1934, to 1936)

TABLE II  
*Influence of Undernutrition on Cardiac Output and Work of Heart (H. F., Male, Aged 40)*

| Diet Calories | B. M. R. Per Cent | Pulse Rate | Blood Pressure |           | Cardiac Output Liters. Min. | Cardiac Work KG. M./Min. |
|---------------|-------------------|------------|----------------|-----------|-----------------------------|--------------------------|
|               |                   |            | Systolic       | Diastolic |                             |                          |
| 800           | -30               | 58         | 96             | 65        | 2.76                        | 3.0                      |
| 2,000         | 5                 | 71         | 128            | 86        | 4.15                        | 5.9                      |
| Change        | 25%               | -18%       | -25%           | -24%      | -32%                        | -49%                     |

method of treatment it has been only 20.7 per cent. (TABLE I). Excluding deaths occurring in the first 24 hours, the mortality rate has been halved, *i. e.*, from 33 per cent. to 16 per cent., and considering the mortality of the first attack alone, the rate has actually decreased to less than one-third, *i. e.*, from 36 per cent. to 10 per cent. Since the only change in the method of treatment in the latter period (1934-1936) had been the institution of undernutrition, it would seem logical to conclude that the improved results may be due to the low calorie regimen. The mortality rate of American and foreign authors for all attacks reported in the literature of the past few years ranged from 38 to 53 per cent., whereas that of Master and his coworkers was 16.5 per cent.; and for the first attack only, the former's rates were 24 to 35 per cent. as against 8 per cent. in the latter's cases.

The **undernutrition therapy** eliminates gastroduodenal reflexes, minimizes the rise in metabolism and cardiac output which usually follows a meal, and

gradually lowers the basal metabolic rate, which effects a decrease in pulse rate and blood-pressure, and so a diminution in the work of the heart. In a patient with a cardiac output of 2.76 liters per minute (TABLE II) after the basal metabolic had dropped to -30 per cent., on an increased diet the basal metabolic rate rose to -5 per cent. and the cardiac output to 4.15 liters per minute. S. Dack (J. Mt. Sinai Hosp. 3:74 (July-Aug.) 1936). The pulse rate which had averaged 58 on the low diet rose to 71; the systolic blood-pressure increased from 96 to 128 mm., and the diastolic from 65 to 86 mm. Hg. From these observations it was calculated that during the low calorie intake the work of the heart was reduced 49 per cent. No ill effects were observed in any case following the low calorie diet.

#### MYOCARDIAL INFARCTION.

—**Symptoms.**—In a review by J. Edeiken and C. C. Wolferth (Am. J. M. Sc. 191:201 (Feb.) 1936) of approximately 100 cases who had survived attacks of myocardial infarction, 14 were

found with *persistent pain in the shoulder region*. In 3 cases the pain developed almost coincidentally with the acute coronary attack, in 4 within 4 weeks, and in the remaining 7 it appeared from 1 to 4 months later. Usually the left shoulder was involved, although the right may also be affected; it may shift from one shoulder to the other, and occasionally it may be greatest in the region of the biceps or deltoid muscles. The pain, usually described as burning, aching or wrenching, may be mild or severe. It lasted from 7 weeks to more than 5 years. As a rule, ordinary movement did not aggravate the pain, but in a few patients it seemed to be increased by exaggerated movements of the shoulder. With the exception of 2 patients, with so-called "trigger zones" over the back of the shoulder, no tenderness on pressure was elicited in the region of the shoulder, arm or back.

Search for a noncardiac cause of the pain was negative. It seemed to bear a closer analogy to causalgia than to any other recognized type of pain, although the usual trophic and vasomotor changes with this condition were not observed; furthermore, hyperesthesia was present in only 2 cases. The time relationship of onset of the pain to occlusion of a coronary artery suggests that the cardiac lesion is an important etiologic factor. Treatment for relief of pain proved singularly ineffective. Deep x-ray therapy was tried in several cases without consistent results.

**ELECTROCARDIOGRAPHY.—FOUR-LEAD ELECTROCARDIOGRAM IN NORMAL MEN AND WOMEN.**—The maximum, minimum, and average measurements of the various wave voltages and intervals in the electrocardiograms of 200 *normal men and women*, ranging in age from 20 to 35 years (below the period of signifi-

cant arteriosclerotic disease), have been tabulated by R. A. Shipley and W. R. Hallaran (*Am. Heart J.* 11:325 (Mar.) 1936). No one with a history of cardiac disease, rheumatic fever, or poor exercise tolerance was included; all were examined for abnormal physical signs; the blood-pressure of all subjects was below 135 systolic and 90 diastolic; a moderately loud systolic murmur was audible over the pulmonic area in about 6 per cent., but no individual with any other frank murmur was included. The precordial lead was taken with the "indifferent electrode" applied to the left leg (referred to as Lead IV by the authors).

Males were found to have higher voltages of QRS and of T than females, both in the conventional three leads and in the chest lead. The average amplitude of the highest QRS in Leads I, II, and III for males was 12.4 mm., for females 10.8 mm.; the average amplitude of T was 3.3 mm. for males and 2.6 for females. Slurring and notching of QRS were common in Leads III and IV, were occasionally seen in Leads I or II, but were not encountered in Leads I and II together or in all three limb leads.

A "deep" Q-wave in Lead III (according to the criteria of Pardee) was present in 4 records, which were in the male group. In one case there was left axis deviation, in another a border of left axis deviation, in a third a border of right axis deviation, and in the fourth no axis deviation was present. T<sub>3</sub> was inverted in 3 of the records, and diphasic in the fourth. The x-rays revealed hearts of normal shape and size, with an anatomical axis within the average range in 2 cases and a slightly horizontal axis in the other two. In all cases the chest was relatively broad, and the individual was inclined to be stout; but the diaphragm was not considered elevated by the roentgenologist.

The conformation of *QRS in Lead IV* was usually of the Q-R diphasic type, but the following exceptions occurred: In 8 instances there was only a simple monophasic downward excursion and in 4 others there was an initial R-wave as high as 3 mm. followed by a deep S-wave. An "M" complex with small initial and terminal positive deflections and a deep negative middle stroke was encountered 17 times. Thus, in 15 per cent. of cases the QRS configuration was not of the usual diphasic type and, although there never occurred a complex with an absent Q-wave and a high initial deflection (above 3 mm.), as is encountered in myocardial infarction, the statement cannot be made that the initial deflection of QRS normally is invariably downward in the leg-apex lead. In 30 cases in which the anteroposterior lead was used, the QRS complex was always of the simple Q-R type.

Frank right axis deviation was not encountered, although approximately 10 per cent. of records showed definite left axis deviation (angle less than  $+30$  degrees).

Slight deviations of the S-T level were common. The limits of deviation measured from the P-R level were 1 mm. above this level and 0.5 mm. below in Leads I, II, and III, except in cases of a deeply depressed P-R level, when the elevation sometimes slightly exceeded 1 mm. The limits of deviation in Lead IV (left leg and apex) were 0.6 mm. above the line and 2.0 mm. below. There were no instances of definitely inverted or diphasic T-waves in Leads I or II, although 35 per cent. of the records had inverted T-waves in Lead III. The T-wave in Lead IV was invariably inverted.

As shown in this study, the character of a chest lead tracing may be affected when the posterior lead is exchanged for a lead from the left leg. The chief differences encountered when such a shift

was made were changes in the polarity of the P-wave, decrease in wave voltages, and frequent departure from the simple Q-R type of QRS complex, so that there was occasionally a small initial upward deflection before the usual deep downward excursion.

**ELECTROCARDIOGRAMS ON NORMAL CHILDREN.**—The findings in 1276 electrocardiograms on 167 healthy children (85 boys and 82 girls, ranging in age from 3 weeks to 12 years) have been reported by C. T. Burnett and E. L. Taylor (*Am. Heart J.* 11:185 (Feb.) 1936). The average number of records on each child was 7.6 in a study of  $5\frac{1}{2}$  years. The P-wave showed higher and lower amplitudes than in the adult; diphasic forms occurred in Leads II and III and notched forms in all leads. Q-waves were deeper in boys than in girls, and there was a more gradual decrease with age in girls than in boys. R-waves may be higher or lower than usual adult standards. R-waves showed slurring in 457 (35.8 per cent.), and notching in 56 (4.38 per cent.).  $R_2$  alone presented M and W forms and "inversion." It was difficult to classify portions of the QRS complex. S-waves decreased with age in all leads. Well-defined and frequently high T-waves were observed in Leads I and II;  $T_3$  was usually of low voltage; inversion was seen only in  $T_3$ , occurring in 242 cases (18.9 per cent.).

Transmission time (PR and QS intervals) was shorter in hearts of children. The ST interval showed a definite lengthening with age. Heart rates decreased with age. Sinus arrhythmia was shown in 279 (21.8 per cent.), occurring most frequently in the tenth and eleventh years. The greatest number of instances of right axis deviations was found in the first 3 months of life, with a noticeable decrease in the period of from 4 to 6 months. Left axis deviation occasion-

ally occurred in average healthy children. This study indicates that normal standards must allow a wide range of individual variations in the electrocardiograms of healthy infants and children.

**Lead IV Electrocardiogram in Children.**—In a study of H. Rosenblum and J. J. Sampson (*Am. Heart J.* 11:49 (Jan.) 1936) of Lead IV of the electrocardiogram in a group of 50 normal children, varying in ages from 1 month to 16 years, 64 per cent. of the tracings showed an upright  $T_4$ -wave; 32 per cent. exhibited a diphasic or an isoelectric  $T_4$ , and in only 4 per cent. of the cases was  $T_4$  inverted. The right arm electrode was placed over the left second, third, and fourth sternocostal junctions, and the left arm electrode over the sixth to eighth thoracic spines on the posterior chest wall. No relationship between the direction of the electrical axis and that of the  $T_4$ -wave was discoverable. In view of the regularity of its occurrence, an upright  $T_4$ -wave cannot be taken to indicate cardiac disease in normal children, although, on the other hand, an upright  $T_4$ -wave is extremely uncommon in the electrocardiograms of adults without cardiac disease.

Also M. Robinow, L. N. Katz and A. Bohning (*Am. Heart J.* 12:88 (July) 1936) report upright diphasic and polyphasic T-waves in Lead IV to be common in normal children, especially in the younger groups. Electrocardiograms of 61 normal children and 5 adolescents, and also electrocardiograms of 31 children, 4 adolescents, and 10 adults suffering from rheumatic heart disease were studied. The contour of Lead IV in normal children was found to alter considerably in tracings taken a few months apart. Children with active rheumatic heart disease showed higher percentages of upright T-waves in Lead IV than normal children of the same age. The T-wave tends to become in-

verted when recovery from the acute stage sets in, and to become more upright when the disease process becomes aggravated. However, exceptions to these correlations were not uncommon.

Axis deviation to the right is believed to be an important factor but not the only one responsible for the upright  $T_4$ -wave in normal children. Since the heart in the child is more mobile than in the adult, variability of  $T_4$  contour in successive records of the same child is more to be expected than in the adult. The electrical field may be altered by changes in the position of the heart, such as might result from shifts in the diaphragm because of gas or food in the gastrointestinal tract, or from small differences in posture of the body when the records were taken. Upright  $T_4$ -waves tended to be more frequent in children with thin chest walls and narrow thoracic cages.

**UPRIGHT OR DIPHASIC T-WAVE IN LEAD IV.** J. Eidenken, C. C. Wolferth and E. C. Wood (*Am. Heart J.* 12:666 (Dec.) 1936) call attention to the significance of an upright or diphasic T wave in Lead IV\* when it is the only definite abnormality in the adult electrocardiogram. In a group of 26 adults presenting this abnormality, the cardiac diagnoses were as follows: in 17, angina pectoris; in 2, questionable angina pectoris; in 4, old coronary occlusion; in 1, paroxysmal cardiac dyspnea; in 1, rheumatic heart disease; and in 1, congenital heart disease. Only 1 of 200 college students had an upright  $T_4$  with normal limb leads, and he was found to have rheumatic aortic insufficiency. An upright  $T_4$  was found in 10 of 45 women over 60 years of age; all 10 presented other evidences of heart disease. In 81 children, of whom 48

\* The chest lead was taken with the right arm electrode over the apex of the heart and the left arm electrode at the angle of the left scapula.



had rheumatic heart disease and 33 no evidence of heart disease, upright  $T_4$  waves were found in approximately 25 per cent. of each group. A  $T_4$ -wave in Lead IV which was isoelectric, or diphasic, with an upright component of 1 mm. or less, has been seen in patients with abnormal limb lead electrocardiograms in whom the presence of definite heart disease could not be proved. In the absence of digitalis medication, the authors have not seen an upright T-wave in Lead IV of any normal adult, with the anterior electrode placed at the apex.

**LEAD IV IN ANGINA PECTORIS.**—In an electrocardiographic study by H. D. Levine and S. A. Levine (Am. J. M. Sc. 191:98 (Jan.) 1936) of 44 patients, subsequently examined postmortem (17 with evidence of coronary artery disease, 4 with valvular disease, 5 with pneumonia, and 14 with miscellaneous diseases), infarction of the ventricle was present in 12 of 15 cases in which  $Q_4$  was absent; 2 cases with bundle branch block and 1 of tuberculous pericarditis with absent  $Q_4$  showed no infarction. The right arm electrode was placed either at the left sternal border or at the apex. Of 15 cases with a small  $Q_4$  (2 mm. or less), about one-half had myocardial infarction. In 11 cases in which the heart was normal and in 1 with posterior infarction, Lead IV was normal. In 16 of 100 consecutive ambulatory cases of angina pectoris  $Q_4$  was absent, and in 11 of these the customary limb leads were essentially normal. From these observations, the conclusion is drawn that the absence of  $Q_4$  is very helpful in the diagnosis of a previous myocardial infarction, except when bundle branch block is present.

### ENLARGEMENT OF HEART.

- In the Lunnleian lectures for 1936, J. Parkinson (Lancet 1:1337 (June 13); 1391 (June 20) 1936) discusses the

causes of enlargement of the heart and the means of its *ascertainment*. Although the apex beat gives good information about the left border of the heart, it is misleading where there is displacement from any cause; furthermore, it is not always palpable, and it may seem to be

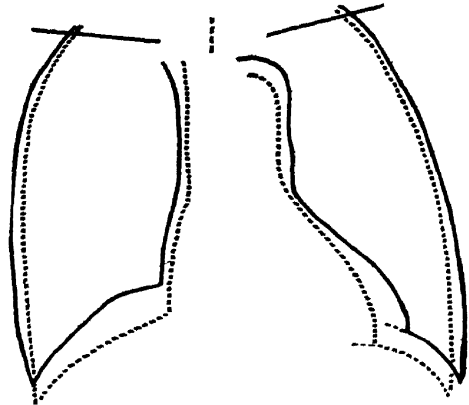


Fig. 1.—Displacement of heart upwards and to left. Pregnancy, ninth month (continuous line); 2 months later (dotted line). (Parkinson: Lancet)

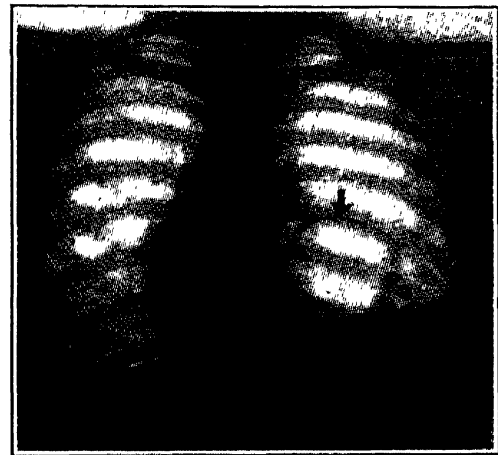


Fig. 2.—Displacement of heart to right by high position (eventration) of diaphragm. (Parkinson: Lancet.)

farther out than it really is when tachycardia is present. The personal factor in percussion is enormous. Cardiometry is too complicated a procedure for routine clinical use, but radioscopy offers an excellent means of study of the heart size without measurements.

While the position of the normal heart in the chest varies considerably, in gen-

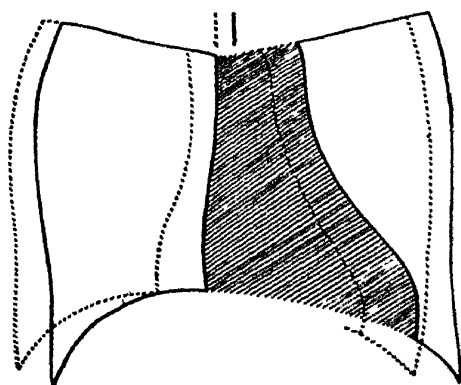


Fig. 3.—Displacement of heart to left by right dorsal scoliosis (shaded portion). Corrected by rotation  $10^{\circ}$  to right (dotted line). (Parkinson: Lancet.)

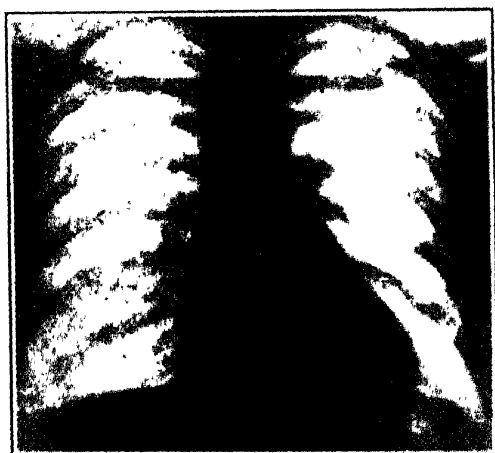


Fig. 4.—Common displacement of heart from slight scoliosis often leading to suspicion of cardiac enlargement. (Parkinson: Lancet.)

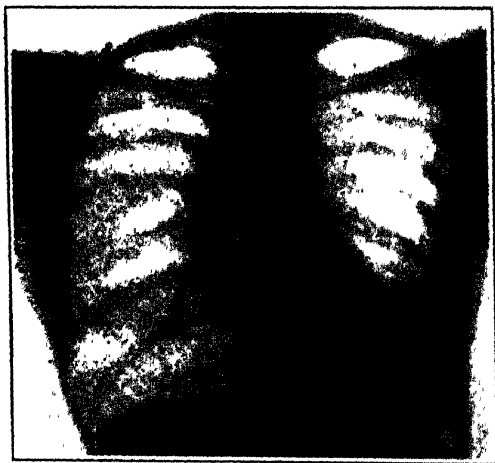


Fig. 5.—Considerable displacement of heart from scoliosis; apex in left axilla. Superficial resemblance of dorsal curvature to an aneurism. (Parkinson: Lancet.)

eral about one third of the area lies to the right of the midline and two-thirds to the left, and the diaphragm seems to be the greatest factor in deciding its position. The short, stout individual with a short, wide chest and high diaphragm has a heart tilted upwards and to the left; the tall, thin individual with the long, narrow chest and low dia-



Fig. 6.—Displacement of heart to right (partial dextrocardia) from scoliosis of rare type, i.e., left dorsal convexity. (Parkinson: Lancet.)

phragm has a heart swung in toward the middle line. The heart of the one looks large and horizontal; of the other small and vertical. Abdominal distention with upper displacement of the diaphragm displaces the heart upward and outward so that it seems larger, while diaphragmatic hernia displaces it to the right. (Figs. 1 and 2.)

Slight dorsal *scoliosis* of the common type, i.e., with convexity to the right, may cause displacement and apparent enlargement of the heart (Figs. 3, 4, 5), and unless this fact is realized, errors will occur. Scoliotic displacement of the heart to the right, produced by dorsal convexity to the left, the rare type of scoliosis, will scarcely be discovered except by radiology. (Fig. 6.)

*Adhesive pericarditis* (nonconstrictive) usually causes no cardiac enlargement. Enlargement when present is referable to the associated cardiac disease. Likewise, *constrictive pericarditis* may cause constriction of the heart, especially of the superior and inferior venæ cavæ, but only occasionally is the heart enlarged. Usually the clinical picture is that of a state of congestion without cardiac failure. *Calcified pericardium* is demonstrable by x-ray (Fig. 7) and is evidence of longstanding adhesive pericarditis, but usually there are no symptoms and no cardiac enlargement. Furthermore, *mediastinopericarditis* with extensive adhesions is of little significance. In the past, the presence of considerable or gross cardiac impairment of the heart has been too frequently attributed to adherent pericardium.

*Acute dilatation* of the heart has gradually lost significance in a clinical sense, as it is now never maintained that heart failure is due to acute dilatation or synonymous with it. "Acute dilatation" from exertion appeals more to the lay than to the medical mind. Medical opinion is now firmly opposed to the idea that a healthy heart in a healthy man can be injured by a physical strain. There may be temporary adjustments of heart size during exertion, but the immediate effect of exercise on the heart's volume is insignificant, even when the exercise has been extreme and prolonged. The heart of an athlete may be somewhat larger than the average in relation to body weight; however, such enlargement is not to be regarded as abnormal, rather it may be counted supernormal, *e. g.*, in Marathon runners. In a follow-up study of the crews of the first 24 Oxford and Cambridge boat races up to 1869, there was little appreciable difference in the mortality from heart disease among them when

compared with men of corresponding age. With persistence of an attack of *paroxysmal tachycardia*, *auricular fibrillation* or *flutter*, enlargement of the heart may occur with evidence of cardiac failure in all its stages. The rapidity of the cardiac enlargement which may take place in the course of *acute cardiac rheumatism* is of interest, though its

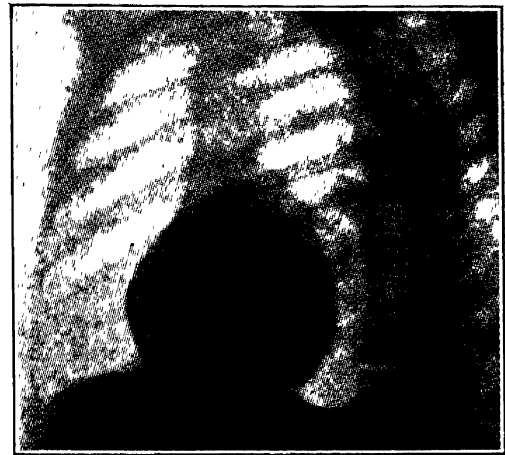


Fig. 7.—Calcification of pericardium. Left (11) oblique position. (Parkinson : Lancet.)

degree and frequency are far from being known. Confusion with pericardial exudate, the part played by a previous attack and early mitral stenosis is always difficult to exclude or appraise when considering enlargement from myocarditis alone. In *acute congestive heart failure* there is change in shape and position of the heart rather than change in size (Figs. 8 and 9). One of the early effects of failure is elevation of the diaphragm from hepatic and other abdominal distention; also, hydrothorax may have a marked effect upon the apparent size of the heart. Such enlargement of the heart as does occur in failure is mostly from congestion, producing the so-called mitralization of the heart.

Starling showed that dilatation of the heart is an essential physiological adjustment to increased work. *Hyper-*

*trophy* may then follow to meet a persistent demand on the heart, as in the overloading of hypertension or valvular disease. Toxic substances are said directly to stimulate the heart muscle fibers to hypertrophy, and prolonged thyroid feeding to lead to hypertrophy.

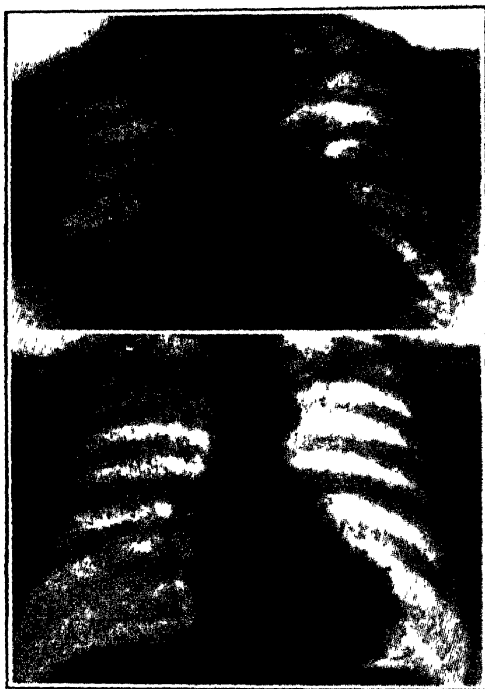


Fig. 8.—Hypertension. Congestive failure. Note raised diaphragm, horizontal heart, congestion of hilar vessels. (Parkinson: *Lancet*.)

Fig. 9.—Same patient. Recovery from congestive failure. Note descent of diaphragm, more vertical heart, absence of hilar congestion. (Parkinson: *Lancet*.)

Hypertrophy may also result from arteriovenous aneurism, narrowing of the coronary arteries, and severe anemia.

Studies of the inflow and outflow tracts in the heart show that dilatation and hypertrophy of the right ventricle begins in the outflow tract and is characterized by lengthening of the anterior portion of the ventricle, with consequent increased prominence of the conus and some levorotation of the heart on its long axis. Late stages of hypertrophy and dilatation of the right ventricle involve the posterior and apical portions,

and the ventricle broadens. Only with the supervention of congestive failure does the right auricle and eventually the left ventricle show consequent change. These principles are applicable also to dilatation and hypertrophy of the left ventricle, where lengthening of the out-



Fig. 10.—Mitral stenosis. Telecardiogram, right 45° oblique position. Barium in esophagus passes over aortic arch, and then held up by enlarged left auricle which projects into posterior mediastinum. (Parkinson: *Lancet*.)

flow tract with early change in the sub-aortic region occurs though it is less easily demonstrated than in the right ventricle.

In continuation of the discussion Parkinson (*Ibid.* 1:139) (June 20)

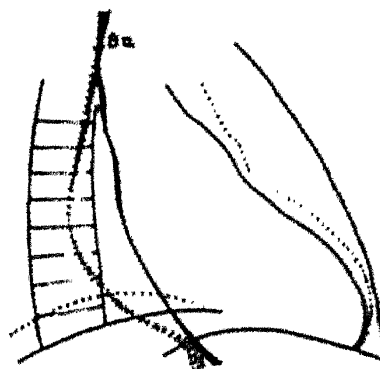


Fig. 11.—Auricular fibrillation without mitral stenosis. Enlargement of left auricle outlined by barium in esophagus (continuous line), and greater enlargement, 6 years later (dotted line). (Parkinson: *Lancet*.)

1936) states that the x-rays make it possible to identify particular enlargement of the various chambers of the heart and of the great vessels.

*Left Auricle.*—The left auricle lies against the esophagus and descending aorta which separate it from the spine. It is not visible from the front, excepting the portion of the left auricular

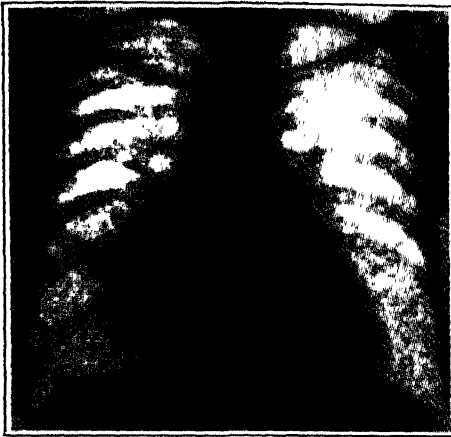


Fig. 12.—Mitral stenosis. Teleradiogram, anterior view. Left border is straight from aortic knuckle to apex from filling out by pulmonary artery and conus. Bulge on right border caused by enlargement of left auricle to right and behind right auricle. (Parkinson; Lancet.)

appendage which adheres to the left border just below the pulmonary artery. It is beyond the reach of percussion, but x-rays in the right oblique position show it well, and its posterior border is conveniently outlined by barium in the esophagus. After the presystolic murmur, this is the most certain sign of mitral stenosis. It is the abruptness of the displacement of the barium stream as well as its degree which is characteristic; and often the barium is held up in triangular form at the upper end of the left auricle before slowly passing this obstruction in a thinner stream (Fig. 10). Auricular fibrillation of long standing and complete heart block may cause similar changes in the left auricle (Fig. 11). Every grade of left auricu-

lar enlargement may be found in *mitral stenosis*. When this auricle enlarges, it nearly always enlarges to the right, so that it begins to appear on the right border of the heart at a little higher level than the right auricle, the border of which it gradually passes (Fig. 12). Extreme enlargement allows extension of the left auricle to the right axilla, where it has even been tapped in mistake for a pleural effusion (Fig. 13).

*Left Ventricle.*—As the left border of the heart is formed by the left ventricle, enlargement is often easy to recognize, and displacements are the chief source of difficulty. In health, the apparent size of the left ventricle depends largely upon the height of the diaphragm. Right ventricular *hypertrophy*, whether from extreme pulmonary disease or congenital lesions, can displace the left border of the heart outwards and simulate enlarge-



Fig. 13.—Aneurismal dilatation of left auricle. Mitral stenosis. Auricular fibrillation. Post-mortem control Teleradiogram, anterior view. In right side of thorax left auricle extends to right axilla. (Parkinson; Lancet.)

ment of the left ventricle. *Aortic stenosis* gives a picture similar to that of aortic insufficiency though seldom is the heart so large, and with the latter there is more pulsation both in the heart and in the aorta. In the absence of

ent ductus arteriosus and septal defects, and disease of the pulmonary artery or its tributaries, may give the impression of an enlarged heart. Disease of the pulmonary artery itself includes *atheroma*, both senile and secondary to mitral stenosis or congenital defects, and the rare *syphilitic lesion*. When the finer branches of the pulmonary artery are affected, or at least when there is pulmonary hypertension, the artery enlarges in chronic pulmonary disease; and if the lesion is syphilitic, *Ayerza's disease* in its most typical form may result. *Aneurismal dilatation* of the pulmonary artery is far more often associated with a congenital defect than with syphilis.

*Enlargement of Whole Heart.*—The whole heart may be enlarged in combined lesions, such as *mitral stenosis with aortic insufficiency or stenosis*, in the advanced stages of *congestive failure*, occasionally in *thyrotoxicosis*, in *myxedema*, with *arteriovenous aneurism*, and occasionally in severe *chronic anemia*.

#### *Prognosis of Cardiac Enlargement.*

There is much truth in the statement that the larger the heart, the worse the prognosis, though it could seldom be applied directly to an individual patient. Also, it might be stated, with reserve, that the heart once enlarged is always enlarged. Auricular enlargement is borne better and longer than ventricular. Treatment should be directed to removal or control of the underlying cause.

**ERYTHROCYTE SEDIMENTATION RATE IN HEART DISEASE.**—In a study of 164 cases of heart disease by P. Wood (Quart. J. Med. 5:1 (Jan.) 1936), *congestive heart failure* was found to retard the erythrocyte sedimentation rate regardless of the cardiac pathology, and might, therefore, mask activity of the disease process. Increased sedimentation rates were found

in cases of *active rheumatic carditis*, *syphilitic aortitis*, and *myocardial infarction*; in these instances, as the condition improved, the readings approached normal. The rate was also found to be increased in cases of *interictive endocarditis* and *malignant hypertension*, but the test is of little value in these conditions. *Pulmonary infarction* increased the sedimentation rate. *Angina pectoris* of effort, apart from syphilitic cases, was associated with a normal sedimentation rate; angina of rest usually showed a somewhat increased rate. Normal sedimentation rates were found in cases of *inactive rheumatic heart disease* and *atherosclerosis*. In *hypertensive heart disease*, the sedimentation rate was normal or slightly increased. In the absence of cyanosis, cases of *congenital heart disease* were associated with a normal sedimentation rate, but with marked cyanosis, the rate was abnormally slow. Mild cases of *thyrotoxicosis*, in which cardiac symptoms predominated, were associated with normal sedimentation rates.

**In Acute Cardiac Infarction.** C. Shookhoff, A. H. Douglas and M. A. Rabinowitz (Ann. Int. Med. 9:1101 (Feb.) 1936) found the red blood cell sedimentation time abnormally rapid in 29 cases of acute cardiac infarction. It became rapid between the second and fifth days, and returned to normal between the thirteenth and thirty ninth days. The abnormal sedimentation rate may outlast the return of temperature and leukocyte count to normal by as much as 4 weeks; also it may be abnormal when the temperature and leukocyte count have been normal throughout. The test is of help in cases with a history of angina pectoris, occurring several days or even several weeks previously, which arouses suspicion of a recent coronary artery thrombosis; also, it has proved a sensitive indicator of subsequent thrombosis in the heart or

elsewhere, or of embolus or infection. A patient with an acute coronary occlusion should be kept in bed at least until the sedimentation time has returned to normal. The authors emphasize the importance of a careful search for infection or infarction outside the heart before a cardiac significance is attached to a rapid sedimentation rate.

### EXTRASYSTOLES OF CLINICAL SIGNIFICANCE.

— As pointed out by E. P. Boas and H. Levy (Am. Heart J. 11:264 (Mar.) 1936), extrasystoles may offer valuable evidence of *myocardial damage or strain*, and their discovery should always lead to a careful cardiovascular examination in an attempt to determine their cause. A generation ago the presence of extrasystoles, or premature beats, often led to the pronouncement of a gloomy prognosis. Gradually it was realized that they are frequently found in hearts otherwise normal, and largely by the teachings of Sir James Mackenzie, physicians learned to regard them as innocuous and to ignore them in clinical evaluation. At least 50 per cent. of individuals with extrasystoles have hearts that are normal, as well as can be determined.

Extrasystoles arise supposedly from an irritable focus in the auricular or ventricular myocardium. Commonly they result from tobacco, coffee, or digitalis intoxication. Occasionally they occur in association with *gall-bladder disease* or with *gastrointestinal disturbances*, being toxic or reflex in origin. Their sudden appearance accompanying an *acute infectious disease* indicates that the heart muscle has been damaged by the toxin or virus of the disease. Auricular extrasystoles occurring in patients with advanced heart disease, particularly with *mitral stenosis*, are usually forerunners of auricular fibrillation. Multifocal extrasystoles, *i. e.*, extrasystoles arising

from different foci in the auricles and ventricles, are usually associated with severe *myocardial disease*.

Numerous extrasystoles occurring in patients with *coronary sclerosis* usually indicate a progressive vascular lesion. At times in *angina pectoris*, extrasystoles appear shortly before the onset of pain, and disappear shortly after the cessation of the exercise that provokes the pain. In individuals with normal hearts or with valvular disease there is a diminution in the number of extrasystoles during the deceleration after exercise, while in patients with coronary disease the extrasystoles are increased in number with exercise. Short runs of extrasystoles or multifocal extrasystoles in coronary sclerosis may be followed by ventricular tachycardia or fibrillation; in such cases the prophylactic use of **quinidine sulphate** is indicated. Extrasystoles occurring with heart rates above 110 are usually indicative of *myocardial disease*. Extrasystoles in patients with active *Graves' disease* usually point to an accompanying cardiac lesion. Extrasystoles occurring without any of the associations mentioned are of no clinical significance.

### CARDIAC EDEMA.—Treatment.

— The therapeutic value of an organic **mercurial diuretic (novurit)** which can be given as a **suppository** has been investigated by J. Parkinson and W. A. R. Thomson (Lancet 1:16 (Jan. 4) 1936). According to the manufacturers, this suppository contains 0.5 Gm. ( $7\frac{1}{2}$  grains) of novurit, a compound akin to salyrgan, combined with 5 per cent. of theophyllin, in cocoa butter. Novurit may be given intravenously or intramuscularly in doses of 1 to 2 c.c., each c.c. containing 0.10 Gm. ( $1\frac{1}{2}$  grains) of the mercurial salt and 0.05 Gm. ( $\frac{5}{6}$  grain) of theophyllin. In a study of 10 cases of congestive heart failure with edema, the average 24 hours'

excretion of urine per dose was for the suppository 2470 c.c. (82.3 oz.), for novurit intravenously 3435 c.c. (114.5 oz.), for salyrgan intravenously 2600 c.c. (86.6 oz.). The previous administration of ammonium chloride resulted in an increased diuresis with the suppository, as also occurred with novurit and salyrgan intravenously.

The patient was kept in **bed**, and a **low-salt diet** was ordered from the outset, with a daily **fluid intake restricted** to 20 to 30 oz. (600 to 900 c.c.). For the first 3 days, or until the urinary output was steady, no treatment beyond rest was given. **Ammonium chloride** was given only for the 24 or 48 hours preceding the administration of the mercurial preparation. In most cases, it was given for 48 hours—120 grains (8 Gm.) during the first 24 hours and 90 grains (6 Gm.) during the second. In the few cases where it was given for 24 hours only, the dose was 120 grains (8 Gm.). The salty taste was disguised with licorice extract or by the sucking of a lemon.

With the suppositories, 68.7 per cent. of the diuresis occurred within the first 12 hours, while the corresponding figure for salyrgan intravenously was 81.7 per cent. The diuresis did not extend beyond 24 hours. No toxic or irritative effects of the suppository were detected. Free evacuation of the bowels is desirable though not essential, and if an aperient is necessary, it should be given 48 hours before the suppository.

In a study of 25 patients with edema, at the Peter Bent Brigham Hospital, M. N. Fulton (New England J. Med. 214:1092 (May 28) 1936) found **mercurin suppositories** to be an effective and safe diuretic, producing results comparable with those obtained by the intravenous injections of salyrgan or mercupurin. Following a period of several days' observation, to allow for

adequate digitalization or a spontaneous diuresis, the patients were given 1 Gm. (15 grains) of **ammonium chloride** 3 or 4 times a day. After 2 to 4 days of this regime, the suppositories were administered usually the first thing in the morning following a cleansing enema. Use of the suppositories was repeated at intervals of 4 to 6 days, the patients, meanwhile, continuing on a daily dosage of 3 or 4 Gm. ( $\frac{3}{4}$  to 1 dram) of ammonium chloride.

Each suppository, made of cocoa butter base, contained 500 mg. ( $7\frac{1}{2}$  grains) of the mercurial salt of mercupurin ( $C_{14}H_{24}O_5N_2HgNa$ ) without any added theophylline, which is approximately 5 times the amount of mercury contained in 1 c.c. (16 minims) of mercupurin or salyrgan. A few individuals complained of slight rectal irritation and burning for 15 to 30 minutes after the insertion of the suppository. After use of 1 to 15 suppositories, in no instance were toxic effects observed either in the patient's condition or by changes in the urine or kidney function tests. Four patients with ascites and edema with cirrhosis of the liver failed to respond with satisfactory diuresis.

The simplicity and ease of administration renders this form of therapy very suitable in the treatment of edema in which the use of diuretics is indicated.

**CARDIAC PSYCHOSES AND NEUROSES. — PSYCHOANALYTIC OBSERVATIONS IN CARDIAC DISORDERS.** As stated by K. A. and W. C. Menninger (Am. Heart J. 11:10 (Jan.) 1936), the lack of coöperation between cardiologists and psychiatrists is deplorable, because it hinders both of them and retards scientific knowledge. The cardiologists acknowledge the need for psychiatric help in complete understanding of their cases,



and the psychiatrists would profit greatly to learn more of the ways in which thwarted instinctive demands are organically rather than behavioristically expressed. The greatest single subject in the more definitive recognition of specific emotional factors and vectors is the appreciation of Freud's concept of the unconscious. Intuitively every thoughtful person is aware of the existence of unconscious emotional factors in his thinking, acting and feeling, but there are strong repressive forces striving to deny it the consideration it deserves. Moreover, physicians in particular have been traditionally educated to distrust their intuition. The practical difficulties in carrying through a thorough psychoanalytic investigation are great; therefore, it is only an exceptional case in which the *emotional life* of the cardiac invalid is studied beyond the superficial descriptive phase. In some instances it appears to relate so specifically to the illness that it seems as if the emotional factors enter into the etiology of the illness.

Many patients are seen whose chief symptoms seem to be referable to the heart. The presenting symptoms of precordial pain, dyspnea, palpitation and tachycardia engage the patient's attention, and he, in turn, uses them to engage the physician's attention—serving as a passport to the land of illness. Some of the alarming cases have been in part the result of unfortunate suggestion of the well meaning physician, who himself alarmed at some of the symptoms, prophesied a serious outcome, or showed so much solicitude and anxiety over their discovery as to gratify to the fullest extent the patient's hopes and fears. Occasionally, some conscious reason exists for the fear and for the excessive need for the protection afforded by the physician; and occasionally, also, organic factors are actually present and

advanced to such a point where even the discovery and correction of the emotional factors is of secondary importance.

While the psychoanalytic studies of cardiac cases are too few for any definite conclusions, it appears that heart disease and symptoms are (sometimes) a reflection of strongly aggressive tendencies which have been *totally* repressed. Characteristically they appear in a man who was strongly attached emotionally to his father and often hostile to his mother. The conscious affection for the father completely obliterated the deeply buried hostilities for him. If, then, the father has heart disease or symptoms of heart disease, it is typical for the patient to include these symptoms in his identification with the father but to carry out the inexpressible patricidal impulses reflexively by unconscious focal suicide. It has been suggested by some analysts that this identification is not with the father so much as with the father's preferred love object, *i. e.*, his wife, the patient's mother. That the aggressive tendencies seem to be important in the development of heart involvements is supported by the fact that coronary sclerosis is so much more prevalent among men than among women.

#### **CORRELATION OF PSYCHIC AND SOMATIC DISORDERS.—**

The importance of the correlation of the psychic and the somatic symptoms in diagnosis is stressed by J. L. Fetterman (J. A. M. A. 106:26 (Jan. 4) 1936). Not only the local region, but also the central mechanism must be considered. The diencephalon—connected with the cortex, midbrain, pons and spinal cord—contains the centers for the autonomic outflow; through the diencephalon and the vegetative pathways every human emotion is "physiologized." At times, organic disease is over-shadowed by psychic complaints or by social catastrophes, a marked fear reaction may be

the responsible factor. In other instances, any lesion or virus may directly or reflexly disturb the diencephalon and cause visceral symptomatology which may be mistaken for a neurosis.

It is generally accepted that organic disease may cause or appear as psychic disorder, and that psychic and somatic disorders may coexist independently; but the fact that psychic disorders produce

decision causes insomnia, and fear spreads through the autonomic system to upset any and all of its functions.

Neuroses are of many types and have many causes, and whether Meyer's psychobiologic concept, Freud's psychoanalytic theory or some other is accepted, the patient exhibits a lack of the integration possessed by the average normal individual; his activity is diverted

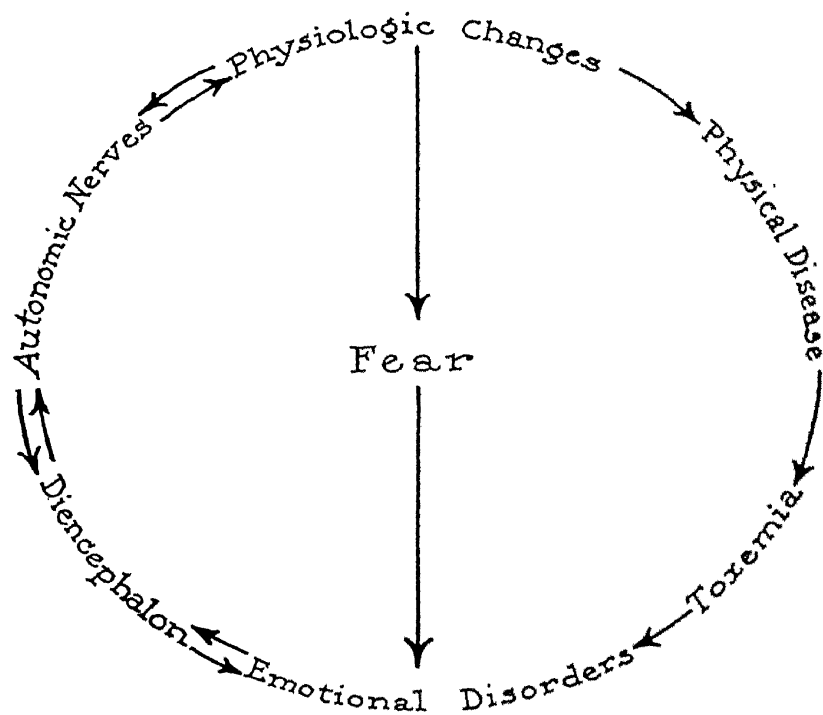


Fig. 17.—Correlation between psychic and physical, "forming a vicious cycle forged by fear."  
(Fetterman: J. A. M. A.)

physiologic and even structural abnormalities has not received sufficient attention. However, many cases are recorded in which psychic factors have caused profound digestive disturbances, affections of skin and liver, or other derangements of visceral function. Cardiac disorders may be among the earliest symptoms of psychotic illness. Definite changes in the functioning of the vegetative system accompany psychoses: conflict causes dizziness, discouragement, disturbance of the cardiac cycle; despair deranges digestion; shame alters the skin color; tension induces tremors; in-

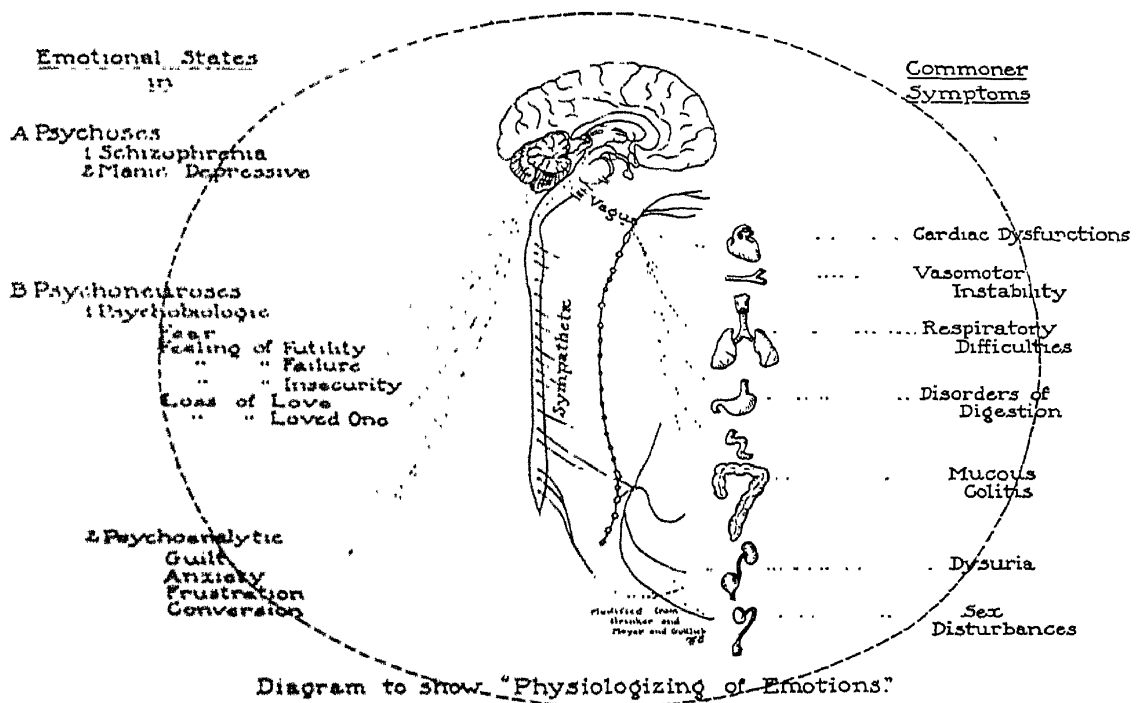
through vegetative patterns; cortical control is poor. Increased sensitiveness, introspection, suggestibility all generate fear; and neurotic symptoms seemingly form a vicious cycle forged by fear (Fig. 17). Visceral changes may serve the ego usefully by exciting interest in bodily disturbances, screening deeper emotional strains from the patient and society. The neurotic illness serves as a flight from reality, a compensation for inferiority, and a source of sympathy and sometimes also financial gain.

The reality of neurotic symptoms, however unphysiologic they seem, must

be accepted, for through the autonomic system actual physiologic and even tissue changes may take place (Fig. 18). Certain characteristics common to neurotic symptoms nevertheless reflect their central origin; they are "widespread, polysystemic, substitutive, ominous."

**CARDIAC PSYCHOSES AND NEUROSES.** As pointed out by J. C. Yaskin (Am. Heart J. 12: 536 (Nov.)

The *treatment* of cardiac psychotic reactions includes: (1) the **removal or reduction of exciting causes**. It is well to bear in mind the sensitivity of some individuals to certain sedatives and somnifacients, the cumulative effects of bromides, and, especially, the sensitivity to combinations, such as amidopyrine and phenobarbital. Disturbances of cerebral circulation may depend upon congestive



(Fig. 18) Correlation between disordered emotional states and commoner neurotic syndromes by way of autonomic nervous system. (Fetterman: J. A. M. A.)

1936), psychotic reactions in the course of *organic* heart disease may vary from mild behavior disturbances to severe reactions. The *symptoms* most commonly observed include states of confusion with disorientation, hallucinosis, persecutory trends, and states of psychomotor excitement. The type and severity of the reaction depend upon the prepsychotic personality, upon renal toxemia, acidosis, drugs, cerebral anoxemia associated with congestion, edema and small areas of softening, and in some cases upon enforced inactivity and reflected pain.

failure, which should receive attention. When *occlusions of small vessels* are suspected, **potassium citrate** early and the **iodides** later may prove of value. (2) Some form of regimen and psychotherapy which will depend upon the type of the psychotic reaction and the associated cardiac condition. The danger of self-injury resulting from delirium or emotional depression, with the need of proper supervision and at times of actual restraint, should not be overlooked.

**Cardiac Neurosis.**—This implies a series of complaints referable to the

precordium or to cardiac rate or rhythm, which are only a conspicuous part of the total neurosis. Whether the disease arises as a result of structural changes in the soma, of abnormal chemisms, or of emotional conflicts or abnormal psychic tensions, a change of affect of the individual (the subjective phase) and corresponding changes in the neuromuscular, autonomic, and secretory functions (objective evidences—emotional expression) takes place. Even with painstaking investigation, organic disease may not be correctly diagnosed, and the cases managed as neuroses. For therapeutic purposes the *diagnosis* of psychoneuroses and neuroses implies the absence of any primary structural or chemical disease; the existence, in the majority of cases, of a certain constitutional make-up (the predisposing causes), the occurrence of precipitating or exciting causes, and the formation of symptoms which may be in the psychic or in the physiological sphere or in both. The constitutional factors may be inherited or acquired, frequently as an integral part of the psychosexual development of the individual. Symptom formation results from the action of some exciting cause, such as an injury, infection, a chemical disturbance, or some emotional stress. The *symptoms* may vary in severity from a slight headache, increased fatigability and irritability, to devastating visceral disturbances, intractable insomnia with marked agitation, and alarming loss of weight. Frequently, the clinical manifestations completely overshadow the primary constitutional factors or the immediate precipitating mechanisms. *Anxiety* is the central symptom of nearly all the neuroses and psychoneuroses, and is of fundamental importance in the management of cardiac neuroses.

One hundred cases comprising anxiety neuroses, conversion hysteria, anxiety hysteria, compulsive-obsessive reactions

and neurasthenia have been reviewed by Yaskin from the standpoint of cardiac symptoms, family history, personality, precipitating causes, modes of treatment and end-results.

**Anxiety Neurosis.** Under this heading are included those neuroses characterized by *episodic* occurrence of anxiety, accompanied by definite somatic symptoms, and by complete or nearly complete freedom from all symptoms between attacks. The most common somatic manifestation presented by each of the 9 cases in this group was *palpitation*, accompanied by anxiety, trembling, and general weakness—frequently accompanied or followed by perspiration. The personality make-up is not of particularly great significance. As the most common cause is to be found in irregularities of the sexual act, the treatment consists largely in the removal of the cause, in suggestion, encouragement, and other superficial modes of **psychotherapy**, and in **sedative medication**. In the majority of cases, the results are favorable; in this series, all cases recovered, there being only 1 recurrence.

**Conversion Hysteria.** Under this term are designated forms of psychoneuroses characterized by motor, sensory, visceral, and episodic phenomena (conversion symptoms) accompanied by little or no anxiety, not due to any physical or biochemical abnormality, and traceable to some definite psychogenic cause. Cardiac complaints are not prominent symptoms, consisting of vague precordial pains or a statement by the patient that he has "heart disease" but unaccompanied by any overt anxiety. In 12 patients in this series, 2 complained of heart weakness, 1 of precordial pain, and 2 of "cardiac disease." The family history and the personality of the patient play a considerable rôle. The precipitating causes were related chiefly to marital difficulties, death in the family, or to a

feeling of economic insecurity. Suggestion in some form is probably the first method of treatment; attempts at compromise formation in marital and economic difficulties also require and deserve considerable attention. Nine patients recovered, 3 improved, and only 2 had recurrences.

**Anxiety Hysteria.**—Under this term are designated conditions showing a variety of somatic complaints not due to primary organic or biochemical disturbances, accompanied by diffuse anxiety or by phobic phenomena, and traceable to psychogenic, often unconscious, causes. *Cardiac complaints are fairly constant and often severe.* In the 63 cases in this series, changeability of pulse rate and frequent attacks of tachycardia were observed in 43, actual dyspnea in 13, precordial discomfort in 24, dizziness and especially fear of cardiac death in 18, transient elevation of blood-pressure in 17, and fear of being left alone or going out unaccompanied in 13 cases. Three patients had previously been subjected to subtotal thyroidectomy without any improvement of symptoms. In this group, the family histories indicate a large proportion of *neuropathic and psychopathic ancestry*; and the personality histories indicate a large neuropathic element. The predisposing causes are usually deep-seated, while the precipitating factors are numerous and varied. Even without a deep analysis, only by review of the precipitating factors, it may be observed that these patients have a great deal of distortion in psychosexual development and attitude. In addition to numerous somatic complaints, the presence of diffuse anxiety, and numerous phobic phenomena make the management of these cases trying, requiring a great deal of ingenuity. Eleven patients required hospitalization, as it was impossible to manage them at home. Encouragement, suggestion, and hospitalization were of

limited value. **Compromise formation** is of importance, especially in cases of marital difficulties where the illness of the patient is probably the most important element in the marital infelicity. **Sedative and tonic medication** proved indispensable in most of these cases. Perhaps the single most important therapeutic agent was **partial analysis**; but, because of time consumption, expense and the resistance of a number of patients, it is not always practical. Twenty-one of the 63 cases recovered, 30 improved, and 6 showed no improvement; 18 had recurrences; 6 developed psychoses. Thirteen of the 21 patients who recovered received a partial analysis; among the recurrences not one had partial analysis.

**Compulsive-Obsessive Reactions** (Psychoasthenia of Janet).—Under this term are designated conditions characterized by the existence of irrepressible thoughts and irresistible impulses designed to avoid anxiety, by the patient's recognition of the absurdity of these thoughts and impulses, and by the appearance of anxiety when the patient attempts to "disobey" the thoughts and impulses. Palpitation and a feeling of impending death is the penalty of attempting to disobey the irrepressible thought or impulse. The family history is not predominantly significant, whereas the personality history shows a very definite neuropathic trend. By partial analysis neurotic traits are found to have existed since childhood, but were thoroughly integrated in the personality make-up, and did not produce disabling symptoms until somewhat later in life. The precipitating causes are largely in the psychosexual sphere. In this form of psychoneurosis, *treatment other than a partial analysis is of little value.* However, the patients do have periods of anxiety, when encouragement, suggestion and sedative medication are of

definite value. Of the 13 cases in this series, all received a partial analysis, 2 with the aid of amytal narcosis.

**Neurasthenia.**—By this term is understood a relatively rare disease beginning in early life, lasting with intermissions throughout life, and characterized by abnormal mental and physical fatigability and irritability, various somatic complaints, mental depression, and insomnia. Neurasthenia as a primary disease is to be distinguished from the neurasthenic symptom-complex which is of common occurrence in many and varied somatic, endocrine, and metabolic diseases, as well as in the psychoses, neuroses, and psychoneuroses. Palpitation, precordial discomfort, and "heart consciousness" were present in the 3 cases in this series; all had a neuropathic family history, and all showed temporary improvement with suitable rest regimens and living within the bounds of their physical and mental capacities.

In the *final analysis* the diagnosis and successful treatment of cardiac neurosis depend upon the ability to determine the *etiological factors*, which is not always an easy matter. The high incidence of neuropathic inheritance is in keeping with the civilian types of psychoneuroses. The precipitating factors embrace a wide range of economic, social, marital, and psychosexual components. In anxiety neurosis and conversion hysteria, the causes are relatively superficial, while in anxiety hysteria and compulsive-obsessive reactions they are more profound and are more intimately associated with the psychosexual life. Probably the clinical manifestations result from the cumulative action of various factors. At times, it is difficult to state whether the "precipitating cause" is really a cause or only an evidence of disease, which is particularly true of marital infelicities, which are not in-

frequently determined by the subtle neurotic attitudes of the patient. In a large proportion of the 17 cases of marital infelicity in this series, the neuroticism of the patient was the determining cause of the marital discord. Ego and herd instinct motivations, as observed in economic insecurity; fears of criminal punishment and of social ostracism; "old maidness," and similar related factors play an important rôle as precipitating causes in the psychoneuroses. On the other hand, there is a large proportion of patients in whom the disturbance of the love life undoubtedly acted as a determining cause. Frigidity was encountered in 11 and homosexual trends in 10 cases, occurring almost exclusively in the anxiety hysteria and compulsive-obsessive reaction groups.

Attempts at **compromise formation** proved of definite value in some cases of marital infelicity, in situations associated with a feeling of economic insecurity, "old maidness," fear of ostracism, and in related conditions, the great majority being cases of anxiety hysteria. Appropriate contraception is frequently a relatively simple and beneficial procedure, especially in anxiety neurosis. **Partial analysis** proved of definite benefit in most of the cases of conversion hysteria, anxiety hysteria, and compulsive-obsessive reactions.

Most *recoveries* were attained in the anxiety neuroses in which the causes could be effectively influenced, and least in the compulsive-obsessive reactions which are accompanied by deep, resistive psychosexual distortion. The recoveries in conversion hysteria, treated chiefly by suggestion and encouragement, were good. In anxiety hysteria, the recoveries were better than anticipated, the majority being attained by partial analysis and attempts at compromise formation. *Improvement* was

observed chiefly in anxiety hysteria and in compulsive-obsessive reactions. The failure of improvement in 9 cases (6 anxiety hysteria and 3 compulsive-obsessive states) is ascribed to the severity of the clinical condition, the failure of coöperation or actual resistance on the part of the patient, and probably, what is most important, to a lack of therapeutic acumen on the part of the physician. *Recurrence* was observed in 24 cases, 18 of which were anxiety hysteria. In the majority of instances, the recurrences were traceable to the incidence of new or reactivated precipitating causes, and, in many instances, to inadequate treatment of the preceding attack.

**LYMPHEDEMA OF EXTREMITIES.** After a study of 300 cases of lymphedema of the extremities, observed at the Mayo Clinic, E. V. Allen and R. K. Ghormley (Ann. Int. Med. 9:516 (Nov.) 1935) offer a clinical classification and discuss the etiology, diagnosis, and treatment of this condition. Recent studies of the anatomy and physiology of lymph vessels, as that by C. K. Drinker and M. E. Field (1933), have aided in the understanding of lymphedema.

**Anatomy and Physiology.**—Lymph vessels are closed vessels, with an unbroken endothelial lining, bathed on the outside by tissue fluid. Every main blood vessel has an accompanying lymph vessel. In the leg, there are superficial and deep systems of lymph vessels without any communication between them except through the popliteal and inguinal lymph nodes. In the arm, the superficial lymph vessels empty into the axillary nodes or, much less frequently, into the deltoidopectoral or supraclavicular nodes; the deep lymph vessels run with the large vessels to empty into the axillary lymph nodes, with or without

the intervention of the deep cubital lymph nodes. The superficial and deep lymph vessels are connected at the elbow by the deep and superficial cubital lymph nodes.

If a large lymph vessel is cut, the circulation is carried on by collateral vessels; later, there is a regeneration of the passage between the two cut ends, and the collateral circulation recedes. Collateral lymph vessels develop a few days after ligation of the main trunks. Regeneration of the lymph vessels is rapid; as early as the fourth day, they cross the scar of an incision, and then by the eighth day, regeneration is physiologically adequate. The endothelium of the lymph vessels is more permeable than that of blood capillaries. Active or passive contraction of skeletal muscles plays a most important part in the movement of lymph of man, the valves of the lymph vessels serving as the most important accessory arrangement for moving lymph forward. Lymph contains fibrinogen and prothrombin, but it clots more slowly (from 10 to 20 minutes) than blood (from 4 to 6 minutes) owing to deficiency of thromboplastic substance, ordinarily supplied in a large degree by blood platelets, which are absent in lymph. However, coagulation of lymph occurs whenever cells in contact with the lymph stream undergo necrosis, or whenever lymph stasis and living bacteria in lymph coexist.

**Experimental Studies.**—In 1934, Homans, Drinker and Field produced lymphedema in dogs by the injection of a solution of quinine and a suspension of silica into lymph vessels of several areas, causing a thrombosis of these vessels. A steadily increasing content of protein was found in lymph; the deep layers of the skin and subcutaneous tissues became the sites of an increasing fibrosis. Attacks of acute lymphangitis, with fever and prostration, occurred

spontaneously. Hemolytic streptococci could be recovered from the edematous tissue at the beginning of the attacks but never at any other time. When thorotrast was injected into the edematous legs, the direction in which it flowed depended entirely on gravity; it ran toward the foot just as well as away from it, through capacious, valveless series of pond-like and river-like lymph vessels.

### *Etiology of Lymphedema of Man.*

-Lymphedema of human beings appears to have a multiple etiology. "Lymph stasis occurs primarily as a result of obstruction that is produced by inflammatory or noninflammatory processes, or by lymphagiectasis, which occurs in association with congenital lymphedema. When obstruction occurs, the intralymphatic pressure increases, and causes dilatation of lymph vessels with subsequent insufficiency of the valves, forcing lymph to seek new channels which are supplied inadequately with valves. Since valves are very important in causing the lymph to move centrally, incompetence of the valves causes further stasis of lymph. The protein content of the lymph increases and fibroblasts proliferate rapidly, since the lymph is an excellent culture medium for the growth of fibroblasts. This fibrosis contributes further to lymph stasis. As a result of the increased quantity of lymph in the tissues, attacks of acute inflammation may recur, producing thrombosis of lymph vessels, more stasis of lymph, and, hence, more fibrosis. The cycle, which is a vicious one, consists of stasis of lymph, fibrosis, inflammation with further stasis, and hence, more fibrosis."

**Classification of Lymphedema of Extremities.**—Cases of lymphedema of the extremities may be divided into 2 main groups, *viz.*, *inflammatory* and *noninflammatory*. Such division indi-

cates the original state: lymphedema which is originally noninflammatory, may be complicated eventually by inflammatory changes.

### CLASSIFICATION OF 300 CASES OF LYMPHEDEMA

|   |       |
|---|-------|
| <i>A. Noninflammatory</i>                             |       |
| I. Primary  | Cases |
| Precox  | 93    |
| Congenital  |       |
| 1. Simple   | 12    |
| Familial (Milroy's disease)                           | 0     |
| II. Secondary   |       |
| Malignant occlusion                                   | 32    |
| Surgical removal of lymph nodes                       | 61    |
| Pressure  | 1     |
| X ray and radium therapy                              | 3     |
| <i>B. Inflammatory</i>                                |       |
| I. Primary (single or recurrent acute and chronic)    | 41    |
| II. Secondary (single or recurrent acute and chronic) |       |
| Venous stasis   | 13    |
| Trichophytosis  | 5     |
| Systemic diseases                                     | 5     |
| Local tissue injury or inflammation                   | 33    |
| Filariasis  | 1     |

### NONINFLAMMATORY LYMPHEDEMA.

**Primary Lymphedema.** "*Lymphedema precox*" affected female patients predominantly (87 per cent. of 93 cases), and in the majority of instances (65 per cent.) had its onset between 10 and 24 years, inclusively. The swelling occurs spontaneously, without known cause. Ordinarily, at the onset, a puffiness about the foot or ankle is noticed, which is worse during long periods of activity, during the menses, and in warm weather. Rest in bed and elevation of the extremity produces temporary disappearance of the edema. One lower extremity may be affected exclusively (70 per cent. in this series), or both legs simultaneously, or one may swell months or years after involvement of the other. In some cases the spread of the edema may be rapid, the entire limb becoming involved within a few days or weeks; in many instances, the swelling is limited



to the foot or ankle or does not extend above the knee. Gradually the swelling, whatever its limitations, becomes more marked; elevation and rest in bed cause its reduction but not its disappearance; the smooth skin becomes roughened, and the hitherto soft edema becomes resistant to pressure; there is actual hypertrophy of tissue, and the limb becomes unsightly, ungainly and uncomfortable, with dull, heavy sensation, but no actual pain. Acute lymphangitis and cellulitis occur infrequently (in 13 per cent. of the cases studied). Ulceration of the skin does not occur.

The predominant incidence among females, the onset in the majority of cases during adolescence, and the accentuation during menstruation tend to indicate that the reproductive organs play a part in the etiology. It is possible that the entire explanation rests on a congenital underdevelopment of lymph vessels, or their inability to develop quickly enough to supply adequately tissues that are growing rapidly. Limitation of the disease to the lower extremities indicates that gravity is an important factor in the development.

*Congenital lymphedema* may be either simple or familial—the swelling, usually of one lower extremity, being present at birth. In the *familial type*, known as *Milroy's disease* (1892), several persons in the same family have lymphedematous swelling of one or more extremities. In the 300 cases of this series, there were no instances of Milroy's disease. Familial lymphedema is not Milroy's disease unless the condition is congenital; many cases called "Milroy's disease" are doubtless examples of lymphedema *precox* with a familial predilection. Recent pathologic studies (P. B. Mason and E. V. Allen: *Am. J. Dis. Child.* 50:945 (Oct.) 1935) of tissues removed from patients with congenital lymphedema show that widely

dilated lymph spaces and connective tissue occupy the space ordinarily taken up by subcutaneous tissue.

*Secondary lymphedema* may be the result of occlusion of lymph vessels by metastasis of malignant disease to adjacent lymph nodes. Pressure outside



Fig. 19.—Congenital lymphedema affecting right arm and face of a girl aged 5 years. (Mason and Allen: *Am. J. Dis. Child.*)

the lymphatic trunks occasionally may produce lymphedema. Secondary, non-inflammatory lymphedema may occur in cases of *Hodgkin's disease*, or *lymphosarcoma*, or it may follow *surgical removal of lymph nodes and lymph vessels for malignant disease* distally situated, or for *tuberculosis*. It also may occur after *treatment with radium and x-rays*.

**INFLAMMATORY LYMPHEDEMA.**—Inflammatory lymphedema is characterized by single or recurrent attacks of acute cellulitis and lymphangitis. The contrast between lymphedema of inflammatory origin and of the *precox* type is striking; in the former, progression is by a series of attacks with sudden onset and severe systemic reaction with chills and high fever; in the latter, the history is

merely one of slowly progressive edema. The acute inflammatory attack may be preceded by a short period of distress in the extremity or in its proximal lymph nodes; and in a short time, a small reddened area spreads until a considerable portion of the extremity is swollen, red, hot, and tender, and its lymph nodes are tender and swollen. The high fever lasts for a period ranging from a few hours to 2 or 3 days, with marked malaise, which may continue after the temperature returns to normal. The abnormal condition of the extremity recedes slowly in from 4 to 14 days, but, after all clinical signs of acute inflammation have disappeared, swelling is present in a greater degree than before the attack. The organism chiefly responsible for the attacks of acute inflammation is the streptococcus. The advanced stage of inflammatory lymphedema has been called "*elephantiasis nostras streptogenes*."

The *chronic form* of lymphangitis of the spontaneous type is exceedingly rare. In such cases, the affected leg is persistently warmer than the other, and a reddish discoloration of the skin is present. In many instances, lymphedema following injury or infection develops without the intervention of acute attacks of lymphangitis and cellulitis or of clinical manifestations of chronic lymphangitis, the infection being of a subclinical nature.

*Primary lymphedema* signifies the condition resulting from single or recurrent acute attacks or from chronic lymphangitis and cellulitis not secondary to any known local abnormality, such as venous or lymphatic stasis or extraneous infection. In some instances, the lymphangitis appears to occur in much the same spontaneous manner as tonsillitis or phlebitis; in others, it may be due to infections introduced into the

lymph vessels through minor portals of entry unnoticed by the patient.

*Secondary lymphedema* indicates a condition resulting from lymphangitis secondary to known causes. *Trichophytosis* about the toes may induce recurrent attacks of acute lymphangitis. The inflammation and the resultant edema are ordinarily limited to the foot and ankle. It is not clear whether the trichophytic infection seems to be definitely related to the acute inflammatory attacks. Instances which strongly suggest that the *Trichophyton* is directly or indirectly responsible for the acute attacks are those in which marked evidence of trichophytic infections, such as desquamation and the occurrence of vesicles, precedes the appearance of cellulitis and lymphangitis. *Pregnancy and systemic diseases*, such as influenza, typhoid fever, pneumonia, malaria, and filariasis, may lead to recurrent attacks of cellulitis and lymphangitis, and result in lymphedema. Except in cases of filariasis, it is possible that the original lesion is thrombophlebitis that produces lymphatic as well as venous occlusion (Homans), with subsequent attacks of lymphangitis, and, eventually, clinical lymphedema. *Local inflammation or injury of tissue*, such as contusions, lacerations, and furuncles, most commonly lead to the production of lymphedema through the intermediation of attacks of lymphangitis.

**Differential Diagnosis.** The brawny, indurated skin and the hypertrophied limb of advanced lymphedema bear little resemblance to manifestations of edema in other diseases. When unilateral, it can be distinguished without difficulty from the edema of *general systemic diseases*, such as myocardial failure, nephritis and myxedema; when bilateral, more thorough examination is necessary. *Sarcomas, lipomas, and neoplasms of bone* are almost uniformly

unilateral, causing regional or localized swelling, whereas the edema of lymphatic obstruction is more uniform and extensive. When swelling of an extremity is localized, careful x-ray studies are valuable from a diagnostic standpoint. Enlargement of a limb in *arteriovenous fistula* is associated with dilatation of and increased pressure in the regional veins. Analysis of the blood from these veins reveals an oxygen content approaching that of arterial blood; if the fistula is congenital, or was acquired before longitudinal growth of the bones ceased spontaneously, the limb is increased in length as well as in circumference. In *lymphosarcoma*, enlarged nodes are usually present; and biopsy is invaluable when doubt exists. *Lipodystrophy* is uniformly bilateral, and is usually associated with generalized obesity or obesity about the pelvis; attacks of lymphangitis and cellulitis do not occur in this condition.

The hypertrophied limb, with the thickened skin and firm consistency, characteristic of advanced lymphedema, has little similarity to *deep thrombophlebitis* with edema of softer degree, stasis ulcers, dermatitis and superficial varices. Thrombophlebitis with edema usually occurs in the course of, or following, an illness such as pneumonia or typhoid fever, or follows childbirth or operation. During the acute stage, a dull aching distress occurs in the area of the involved vein, which is tender to pressure; the edema develops rapidly to its fullest extent in the course of hours, and the superficial veins are dilated and the pressure within them is increased. Occasionally, the two conditions coexist; and, in rare instances, it may be difficult, if not impossible, to distinguish between them, although x-ray studies may be of some value.

**Treatment.** MEDICAL. In order to be of value, medical treatment must be

carried out early, when the edema first becomes evident, *i. e.*, before the limb is greatly hypertrophied with connective tissue. The problem consists of causing the lymph to move toward the body by preventing stasis, which is best accomplished by compressing the limb by adequate bandaging. **Elevation of the extremity** until as much as possible of the lymph has been removed is an important first step. Cloth bandages are of little or no value; also, in many instances, elastic stockings are unsatisfactory. A **pure rubber roller bandage 3 inches wide and 5 feet long**, is preferred by the authors. Of the 3 weights available, the proper one depends on the difficulty of controlling the edema. Ordinarily, the bandage is applied over a lisle stocking, beginning by making 2 turns about the foot, 2 figure-of-eight turns about the ankle, and progressing up the extremity to the knee; the toes and part of the heel are left exposed. The bandage should be removed and applied in the same manner each time, as it becomes shaped to the extremity on repeated use. If it is applied too tightly, the toes become discolored, cold, and numb; if applied too loosely, edema results. It should be removed at midday and reapplied over a dry stocking after the patient has rested for an hour. The same procedure is repeated at night if the patient is active. If he remains home, he may remove the bandage and elevate the leg, while sitting. A well-fitting elastic stocking may be used for "dress" occasions. It is well to point out to women that the lymphedematous leg has an abnormal appearance which the bandage increases but little, and to emphasize that uncontrolled edema almost invariably causes a gradual increase in size of the limb. Once every month or so, the bandage may be left off for a day as a trial; if edema reappears, the support must be worn again.

The attacks of *acute lymphangitis* ordinarily subside spontaneously, but recovery is hastened by **elevation of the limb** and the application of **hot moist packs**. When reactions are severe, **streptococcus antitoxins**, such as used in the treatment of erysipelas or scarlet fever, or polyvalent serums may be used. Blood serum from patients who recently have recovered from a similar attack may be of value. The authors have never observed patients to whom it was considered necessary to give antitoxins or **convalescent serum**. Care should be taken to avoid serum reactions. Portals of entry, such as are present between the toes in the presence of trichophytosis, should be removed. When attacks of acute inflammation recur, **trichophytosis** should always be suspected, and vigorously **treated**, if present.

**SURGICAL TREATMENT.**—Selection of cases of lymphedema for surgical treatment depends upon the etiology and severity of the lesion. There is no need for operation in the presence of malignancy, Hodgkin's disease, or pelvic tumors. The patient with mild lymphedema, unfortunately, cannot be promised a great deal of benefit. The leg can be restored to normal size and to nearly normal shape, but there is no assurance that such restoration will be in any way permanent unless an adequate type of **supporting bandage** is worn for an indefinite period. The more severe the case, the more benefit can be offered with surgical treatment.

The immediate *preoperative care* of the patient should consist of **rest in bed** for a few days, with the affected limb **elevated continuously**, in a sling, at an angle of at least 45 degrees, to reduce the edema. Diuretics, such as **salyrgan**, and **firm bandaging** may hasten the disappearance of edema. As

a rule, in 3 to 6 days the amount of lymph in the limb will be minimal.

In this study, the surgical method described originally by Kondoleon (1912), and modified by Sistrunk (1923) has been followed:

The actual operation should be carried out under spinal anesthesia, using a tourniquet, applied as high as possible on the affected limb and usually without the customary towel beneath it. Two incisions are made along one side of the thigh or arm, extending as high as the lymphedema, so that a long strip of skin may be excised in an elliptical manner. The amount of tissue that can be removed will depend on the width of the strip of skin between the two incisions. As much as possible should be removed in order to reduce the size of the extremity greatly. When the incisions have been made through the skin, the margins of skin to be left are undermined for a distance on either side, approximating half of the circumference of the extremity. The skin, subcutaneous tissue, and as much as possible of fascia, except that at the intermuscular septa and at joint capsules, are removed in one piece. Care should be taken not to damage the main cutaneous nerves. After removal of the tissue, the wound should be closed with interrupted sutures. No attempt is made to secure hemostasis, only the larger branches of the veins being ligated. In closing the wound, one should not hesitate to apply as much tension as is necessary; considerable tension may be applied without fear of sloughing. Indeed, it is better to have some tension than to have an excess of skin remaining redundant. A pressure bandage is applied and the tourniquet released slowly, taking several minutes to allow the circulation actually to return to normal. This step is believed to be of considerable importance, as it is possible that the sudden flooding of the circulation with material from the large wound may have something to do with the high incidence of surgical shock. The limbs are not elevated after the operation, so that materials from the wound get into the general circulation somewhat more slowly than if the limbs were elevated. Apparently, as a result of the methods mentioned, the incidence of postoperative shock in these cases has been reduced to almost zero.

After 10 days the dressing is changed, and if healing has advanced sufficiently, the patient is allowed to be up. Adequate bandaging is necessary for an indefinite period. Crutches or

cane are unnecessary when walking is resumed. It is customary to wait from 3 to 6 months between operations, *i.e.*, one side of an extremity is treated and healing is allowed to become complete before operating on the other side. Occasionally, enough improvement results from the operation on one side to justify omitting the second stage, but, as a rule, a much better result is obtained if both sides are subjected to operative treatment.

There is considerable doubt that the benefit which follows surgical treatment results from anastomosis of the superficial and deep lymphatics, as Kondoleon originally intended. The operation appears to be predominantly a plastic procedure, removing large valveless lymph spaces and hypertrophied connective tissue. Perhaps the most satisfactory procedure will be found to be a combination of the plastic operation of Kondoleon and one designed to carry the lymph around the area of obstruction, such as anastomosis of the lymphatic vessels of the extremity with those of the trunk.

J. Homans (New England J. Med. 215:1000 (Dec. 10) 1936) has found that after an effective series of opera-

tions upon the lower leg in lymphedema, the enlargement of the thigh is decidedly reduced and, therefore, operation on the thigh is not essential.

If there is considerable swelling of the *foot*, it may be necessary to perform operations similar to those on the leg, but on a smaller scale, making the first incision across the foot and nearest to the toes, for the flaps turned up upon the foot cannot be immediately adjacent to the lower end of the longitudinal flaps made at the same sitting. Perhaps a week after the first operation upon the anterointernal face of the calf, a second plastic is carried out on the opposite, or posteroexternal face. In the latter, it is important to preserve at least a part of the nerve supply to the heel (the sural nerve), which requires careful dissection. Following the second operation, the patient is sent home wearing a **bandage** and is instructed to keep the **leg elevated as much as possible**. An interval of 2 months or so should probably elapse before the final pair of plastics is carried out.

## ENDOCRINOLOGY

By LEOPOLD GOLDSTEIN, M.D.

### ABORTION, HABITUAL.—

**Treatment.** In the past few years reports have appeared in the *literature* describing cases of habitual abortion treated by **corpus luteum extract**. This therapy is based on the assumption that because of a lack of progesterin (progesterone), the uterine lining is not prepared properly for the normal growth and development of the embryo. As early as 1918, J. C. Hirst employed injections of corpus luteum extract in the treatment of habitual abortion. C. Mazer and L. Goldstein reported fairly successful results obtained by the use of corpus luteum therapy in cases of

repeated abortion. Later, L. Krohn, F. H. Falls and J. E. Lackner reported 19 cases of threatened and habitual abortion treated by corpus luteum extract with successful results in 14.

Recently, H. F. Kane (Am. J. Obst. and Gynec. 32:110 (July) 1936) reported 40 cases occurring in private practice. Cases of threatened abortion and those which presented any demonstrable pelvic disease have not been included in this series. In 20 cases there had been but one previous abortion, and very likely some of these patients would have gone to term without treatment in a subsequent pregnancy.

Thyroid and iodine preparations were also given the patients, as suggested by Mazer and Goldstein. Treatment was begun as soon as the patient appeared for prenatal care. **Progesterone**, in the form of **proluton**,  $\frac{1}{25}$  rabbit unit, was given intramuscularly every other day for 10 doses. This procedure was repeated at 3-week intervals until the end of the fourth month. In addition, the patient is given  $\frac{1}{2}$  grain (0.03 Gm.) of desiccated **thyroid**, 3 times a day, for 2 weeks, and 4 grains (0.26 Gm.) of **sodium iodide**, 3 times a day, for the following 2 weeks; then resuming the thyroid, a change is made to sodium iodide every 2 weeks. At the end of the sixth month, this medication is stopped.

As a result of the progesterone therapy, 36 living children were born. It is interesting to note that in this series there was 1 case of spina bifida, 1 of pyloric stenosis which required operation, and 1 case in which there were present imperforate anus, a congenital heart lesion, and mongolism. Three of the mothers who under treatment produced normal children, had previously borne babies with spina bifida. Moll, Huntington and others have shown that aborted fetuses are almost always defective in some manner. It must be borne in mind that the expulsion of an early deformed embryo may be nature's way to eliminate the possibility of the birth of a deformed child. The question, therefore, has arisen in the minds of certain clinicians of the advisability of too strenuous treatment for threatened abortion in the first two months of gestation in order to save an already damaged fetus. Since the majority of fetal defects occur before the time of placentation the possibility of a fetal defect should be considered when undertaking the treatment of a patient with threatened abortion.

### ACNE VULGARIS. — *Etiology.*

- In recent years the studies made by Bloch and by van Studdiford have produced added confirmatory evidence to support the idea that the underlying cause of acne is to be found in an endocrine imbalance incident to puberty.

Bloch reports the finding of some degree of acne in 59.6 per cent. of girls and in 68.5 per cent. of boys, ranging in age between 6 and 19 years. The study was made on a group of 1000 individuals. It is his belief that the process in the body which is responsible for the occurrence of menstruation and of the growth of pubic hair and axillary hair likewise determines the appearance of acne. C. H. Lawrence and Feigenbaum reported the results of treatment of 15 patients with acne by injection of **antuitrin-S**. Subsequently Lawrence (J. A. M. A. 106:983 (Mar. 21) 1936) reported on a study of 30 patients treated by the same method.

Three-fourths of the patients were between 10 and 20 years of age, and in the remaining fourth the acne had appeared during adolescence in all but two, in both of whom it was preceded by changes in the rhythm and character of the menses. The onset of the eruption was between the twelfth and fourteenth year in more than two thirds of the patients, and in only one did it appear as early as the tenth year. Its severity was rated as mild in 5 patients, moderate in 13, and severe in 12 cases. The eruption was confined to the face in 15 cases, to the face and neck in 2, and in 13 it was distributed over the face, neck, chest and back.

Ten of his patients were males and 20 were females. In the girls a definite history of an exacerbation of the eruption at the menstrual period was obtained in 8 patients; 11 had never noticed any such relation; and 1 stated absolutely that it did not exist.

The menses were normal in only 6 of the 20 females, the remainder having abnormalities of rhythm, duration or amount of flow, or definite dysmenorrhea. Oligomenorrhea was encountered more frequently than any other type of disturbance, but 4 patients had severe menorrhagia.

Genital development as observed in the males was normal in 9 patients. One showed definite genital hypoplasia. Three adolescent girls showed definite genital hypoplasia, and the incidence of oligomenorrhea would suggest its presence in a considerably larger number.

The basal metabolic rate was normal in 18 patients, between minus 10 and minus 20 per cent. in 4, minus 29 in 1, and between plus 10 and plus 20 in 5 cases. The patients with low basal metabolic rate showed no physical or laboratory signs of thyroid deficiency. The fasting blood sugar was normal in all patients.

**Treatment.** The treatment consisted of injections of 2 c.c. ( $\frac{1}{2}$  dram) of **antuitrin-S** every day. Injections were omitted during the menstrual periods, though in no instance has there been noted any effect on normal menstruation. In the patients in whom there was co-existing menstrual disturbance, improvement in both acne and menstruation progressed in equal measure, indicating a general effect on bodily economy rather than one localized in the skin.

The duration and amount of treatment necessary to produce results varied greatly in different patients. The average dosage in the series has been 3360 rat units, the maximum 7700 rat units, in a patient 15 years of age with severe general acne, and the minimum 300 rat units in a patient 30 years of age with a mild eruption confined to the face and neck. No explanation of this variation is yet apparent, though the indications are that it depends on the gravity of the

fundamental imbalance, rather than on its external manifestation. Improvement has been apparent in the majority of patients, in 2 to 4 weeks, and maximum benefit has been obtained in from 12 to 16 weeks. Two patients have shown slight relapses, beginning 4 and 6 weeks after treatment was terminated, and responding promptly to the resumption of treatment. No difference was apparent between the two sexes as regards response to treatment.

The evidence obtained from Lawrence's studies, which brings to light a considerable association of acne with physical sexual retardation and disturbances of menstrual function and of carbohydrate metabolism, furnishes a considerable indication that a hypofunctional disturbance of the anterior pituitary lobe is a factor of importance in the causation of acne. Finally, the response to treatment with anterior pituitary-like substance offers confirmatory evidence of considerable weight.

**ADDISON'S DISEASE.—Pathogenesis.**—The activity of the adrenal cortex related to electrolyte physiology and renal function is discussed by R. F. Loeb, D. W. Atchley and J. Stahl (J. A. M. A. 104:2149 (June 15) 1935). The syndrome of salt loss, dehydration and the resulting shock, is characterized by a group of symptoms similar to the symptom-complex of acute adrenal insufficiency. These symptoms consist of progressive weakness, overwhelming prostration, nausea, vomiting, tachycardia, lowering of the blood-pressure, and subnormal temperature. Loeb believes that the loss of salt and water might be an important factor in acute adrenal insufficiency. In cases of adrenal disease admitted to the Presbyterian Hospital, New York, it was found that there was a marked decrease in the sodium content of the blood together

with a marked dehydration. These patients were relieved by intravenous injections of salt solution without the use of glandular therapy.

**Treatment.**—The treatment of Addison's disease will be successful only when the active principle or principles of the adrenal cortex become available for clinical use in high concentration and in a form within the economic ability of the patients. Loeb and his associates state that they have used a commercial preparation of cortical substance only occasionally, and have noted little objective evidence of a beneficial effect. These writers claim that if adrenal insufficiency in man is not relieved by the administration of salt, it will not be relieved by commercial cortical extracts given in the usual dosage. Their studies indicate that there is a definite relationship between the sodium metabolism and the active substance of the adrenal cortex. In adrenal insufficiency, the sodium concentration of the blood is decreased because of an elevation in the rate of sodium excretion. The administration of **saline** will often alleviate acute adrenal failure and the continuation of **salt** will alleviate the signs and symptoms of Addison's disease. However, when there is marked destruction of the adrenal glands, salt therapy alone will not maintain life.

Sexual functions are usually disturbed in patients with Addison's disease. In women, gonadal atrophy follows as a result of adrenal insufficiency and amenorrhea occurs. H. O. Neumann (Arch. f. Gynäk. 160:481 (Apr. 2) 1936) recently cited a case of a woman with Addison's disease, in whom the cyclic sexual function was disturbed. After treatment with **cortical extract** and with **1-cevitamic acid** the menses returned.

The treatment of Addison's disease is based on two lines: (1) administration of adrenal cortical hormone, and

(2) maintenance of the salt balance of the blood, according to A. Groelmann ("The Adrenals," The Williams and Wilkins Co., Baltimore, 1936). The first requirement of successful therapy must consist in supplying an amount of **adrenal cortical hormone** adequate for relieving the patient of asthenia, gastric disturbances, weakness, etc., and permitting him to perform his normal activities without subjective treatment.

This author further discusses the treatment of Addison's disease: Exhaustive examinations are to be avoided. Transportation over long distances has brought on a severe crisis. Extremes of heat or cold must be avoided. Drugs must be administered very cautiously. Purgation has proven fatal in several cases.

The administration of an adequate supply of the **cortical hormone** should result in an alleviation of the symptoms due to disease of the adrenals. Certain of the bodily deficiencies due to the disease may be remedied by other means. Thus, the diminution in the blood volume which occurs in crises should be corrected by intravenous injections of **glucose and saline solutions**. The rationale of sodium therapy is well established. The loss of this substance from the body in adrenal insufficiency leads to a reduction in its concentration in the body. It is to be expected therefore that the replacement of the lost sodium chloride will aid in preserving the well-being of the patient. The experiments of Harrop and his collaborators would indicate that the use of **sodium chloride together with sodium bicarbonate** is advantageous over the use of the former substance alone. The administration of sodium chloride intravenously to patients in crisis has proven life-saving. Ten to 20 grains (0.6 to 1.2 Gm.) of sodium chloride administered daily has been of great aid during periods of remission from the more



severe stages of the disease. This salt or a mixture of sodium chloride and sodium bicarbonate in the ratio of 2:1 by weight may be administered in enteric coated capsules, in milk, with lemon juice, etc.

Although the results of the therapeutic management of Addison's disease have been exceedingly disappointing in the past, there is every reason to anticipate better results in the future. The combined use of salt and ample doses of a potent preparation of the adrenal cortex (administered orally in frequent doses) should radically improve the poor results hitherto obtained.

**ADRENAL GLAND.—ADRENAL TUMOR.—*Diagnosis.***—The x-ray is a valuable aid in the diagnosis of adrenal tumors and hypertrophy of this gland. It is of especial value in cases in which no palpable mass is present. H. H. Carelli demonstrated that carbon dioxide infiltrated into the perirenal fascia would be of value in the x-ray visualization of the kidney, the kidney capsule, and the adrenal. In 1929, L. Langeron, E. Decherf and Danes showed that an injection intraperitoneally of air would permit visualization of an adrenal tumor.

Recently, G. F. Cahill (J. Urol. 34: 238 (Sept.) 1935) developed a method of visualizing the adrenal by the straight injection of a measured amount of air directly into the perirenal space by hand pressure, with no attempts to measure the amount of pressure. He found that the injected air would more or less slowly infiltrate through the fascial planes, so that x-rays taken 12, 18, 24 or 36 hours later would show the organs and fascial planes very clearly, especially, as desired, around the adrenal.

This method has been found by Cahill to be of value in demonstrating the

pathological, as well as the normal adrenal gland. Of great value is the determination of a normal adrenal shadow on the opposite side when an adrenal neoplasm is present.

The author has noted no ill effects from the procedure. The introduction of air produces a slightly uncomfortable feeling of pressure that rapidly disappears. The technic of Cahill's method of x-ray diagnosis is as follows:

With the patient on his side, the flank area is sterilized. The site of the injection, as well as the tract, is injected with **novocaine**. The trochar is then introduced, usually below the twelfth rib, in an area between the outer border of the erector spinæ muscle and the reflection of the peritoneum. As the trochar passes through the transversalis fascia, the change in resistance is noted; it is then passed a short distance upward and inward. At this point, Carelli found that changes in manometer findings on inspiration and expiration showed if the open end of the trochar was in the renal fascia. This practice has been discontinued. Attached to the trochar is a sterile glass tube filled with sterile cotton as an air filter. This is further connected to a rubber bag and then to a measure pump. Between 200 and 250 c.c. of air, depending on the size of the individual, is introduced into the bag and this is then slowly forced by hand from the bag through the cotton and trochar into the perirenal fascia. A film is then taken and developed. This shows where the air is located. It may then be displaced upward or downward in the fascial planes by manual pressure. The films that have best shown the fascial planes have been those taken 18 or 24 hours later. In these, the air has been well diffused.

**TUMORS OF CORTEX.**—As early as the year 1756, William Cooke reported a case of tumor of the outer layer of the adrenal gland with associated disturbances. Since then, numerous papers have appeared which describe typical endocrine syndromes associated with "functioning" tumors of the adrenal cortex. In 1912, Alfred Gallais described a syndrome called "*le syndrome génito-surrénal*," and in 1921 K. H. Krabbe described a syndrome named "adrenal

hirsutism." This symptom-complex, consisting of hirsutism, obesity, hypertension, osteoporosis, and hyperglycemia, has come to be recognized as the result of adrenal cortical hyperfunction. However, it must be borne in mind that this syndrome has also been encountered in individuals who later did not show, either at operation or autopsy, any pathological abnormality in the adrenal glands. In other cases, the only pathological condition found at autopsy to explain the symptom-complex was a tiny basophilic adenoma of the anterior lobe of the pituitary gland. The possibility has been entertained that a basophilic tumor of the pituitary gland may incite the hyperplasia and growth of adenomas in the adrenal glands.

Harvey Cushing states: "Some of these syndromes have unquestionably been due to corticoadrenal tumors, and in not a few instances, indeed, such a tumor has been removed at operation with definite amelioration of symptoms. What is more, in similar states, suprarenal tumors have been found after death in the absence of any recognizable abnormality in the pituitary body, though all too often the protocol refers to the examination of this structure either in the briefest terms or not at all. While there is every reason to concede, therefore, that a disorder of somewhat similar aspect may occur in association with pineal, with gonadal, or with adrenal tumors, the fact that the peculiar polyglandular syndrome, which pains have been taken herein conservatively to describe, may accompany a basophil adenoma in the absence of any apparent alteration in the adrenal cortex other than a possible secondary hyperplasia, will give pathologists reason in the future more carefully to scrutinize the anterior pituitary for lesions of similar composition."

**Symptoms.** - The symptoms of cortical adrenal tumors depend on the sex, age and degree of malignancy. Cases of adrenal cortical tumor have been reported without any definite chain of symptoms having been produced during life. The presence of adrenal cortical tumor in the male child usually is associated with an increase in muscular development, the so called Herculean type. There is also a marked growth of hair on the face, body and extremities, and a precocious development of the sexual organs.

In the *female before puberty*, there is a change of the physical constitution toward masculinity. Obesity is frequently an accompaniment. There is growth of hair on the genitals, followed by growth of hair on the face, body and extremities. Premature ossification of the epiphyses is frequently noted. There is an enlargement of the clitoris and labia in these children. As a rule, however, menstruation does not occur, although it has been reported in several cases.

In the *female after puberty*, the syndrome known as the "adreno-genital" syndrome, occurs. The first signs of adrenal cortical hyperplasia or tumor are usually disturbances in menstruation. The periods become scanty and later cease entirely. Accompanying the loss of menstruation there is usually loss of libido and sexual desire. Another striking symptom is the abnormal growth of hair. The hair begins to grow on the face, especially on the upper lip and chin. In one of the patients described by G. F. Cahill, R. F. Loeb, R. Kurzrok, A. P. Stout and F. M. Smith (Surg. Gynec. and Obst. 62:287 (Feb. 15) 1936), a girl of 16, the hair was so profuse on the thighs, abdomen, pubis, and anal region, that the skin could barely be discerned through the mass of hair. When the tumor is removed, the hair

falls out and the feminine pubic line is reestablished.

G. F. Cahill states that in cases without endocrine symptoms the tumor, as a rule, has been large enough to be palpable in the abdomen in the region of the kidney. Pain not infrequently is present. The kidney is displaced downward by the tumor. The displacement has been demonstrated by x-rays and particularly by pyelograms. In some cases, invasion of the kidney has been demonstrated by irregular compression changes in the pyelographic shadows in the upper pole.

**Diagnosis.**—Tumors and enlargements of the adrenal have been diagnosed by x-rays, either through the density of the tumor shadow itself, or through the tumor displacing some shadow-forming organ, usually the kidney. Cahill uses the method of Carelli in demonstrating both pathological and normal adrenals. The air injected into the perirenal fascial space was displaced by manual pressure around the adrenal areas, and then upon x-ray examination the air was shown infiltrating around the adrenal and upper pole of the kidney. With this method it is possible to outline the adrenals and with the change in size, shape and position of the adrenal shadows, to obtain a tenable diagnosis of tumor; it is also possible to determine the presence or absence of a shadow of an apparently normal adrenal on the opposite side.

Cahill and his associates (*loc. cit.*) recently reported a study of 10 cases of adrenal cortical tumor. Five cases had proved adrenal cortical tumors; in the other 5 cases symptoms suggestive or characteristic of the disease were present, but there was no demonstrable evidence of tumor.

The following case reported by Cahill is one in which the diagnosis rested between a basophilic adenoma of the

pituitary gland, and bilateral hyperplasia of the adrenals.

The patient was a girl, 20 years old, who complained of obesity and irregular menstruation. She had a normal birth and had had a normal childhood until 12½ years of age, when menstruation began. She began to increase in weight. Her menses were regular for 5

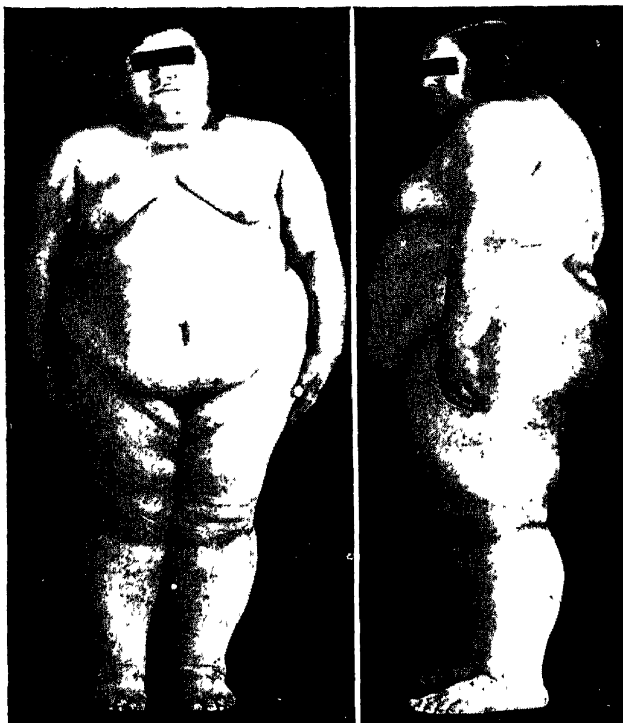


Fig. 1.—Shows obesity and hirsutism. (Cahill, Loeb, Kurzrok, Stout and Smith: Surg., Gynec. and Obst.)

months, and then ceased, and did not recur until 2 years later. She developed a tired and sleepy feeling. She had headaches over the eyes and in the occipital region for the last few years. A heavy growth of hair occurred on the head, eyebrows, on the face and chin, and on the extremities. She suffered from chilly feelings and fainting spells.

She weighed 301 pounds and was 65 inches in height. The pubic hair distribution was masculine. The breasts were medium-sized, and the abdomen was pendulous. Wassermann tests were negative. Blood urea was 12 mg. per liter and blood sugar was 97 mg. per 100 c.c. Basal metabolism rate was plus 22. X-ray film of the skull showed no change in the sella turcica. Examination of the eye-grounds was negative. The blood-pressure was 170/100; pulse averaged 90.

X-ray examination of the adrenals made with air injection showed both adrenals remarkably enlarged, but apparently of the symmetry of normal adrenals. The patient menstruated for 6 days while in the hospital, receiving 10 c.c. (2½ drams) of **antuitrin** during the week. There was no change from normal in the clitoris, labia or pelvis.

**Treatment.**—In the experience of W. Walters, R. M. Wilder and E. J. Kepler, cortical adenoma and hyperplasia of the suprarenal cortex are encountered in a large percentage of cases in which the peculiar syndrome described above is present. **Removal of the adenomas** is highly beneficial, and reduction of the mass of cortical tissue in cases in which there is bilateral adrenal hyperplasia may also be helpful. The adrenal glands can be explored with very little danger and, according to the aforementioned writers, it seems that this should be done in all cases in which the syndrome in question is encountered and a positive differential diagnosis cannot be made. If a cortical tumor is found, it should be removed. If the *adrenal tissue is hyperplastic*, its mass may be reduced by **resection**, with later treatment of the pituitary gland by **x-rays**. They believe this to be a better plan than to reverse this procedure and to depend primarily on treatment directed at the pituitary gland. Treatment of the pituitary gland by x-rays was not effectual in controlling the syndrome in one case in which a basophilic pituitary adenoma was present; it had no effect in another case in which a pituitary tumor was suspected, and could not be expected to be of help in cases in which adrenal cortical adenoma was present.

**TUMORS OF ADRENAL MEDULLA.**—Regarding the function of the medullary portion of the adrenal glands, the general view still holds that the adrenal medulla is relatively inert except under conditions of emotional stress, when it discharges its secretion (E. J.

Kepler; Arch. Int. Med. 56:105 (July) 1935). The relationship of the adrenal medulla and its secretion, epinephrine, to carbohydrate metabolism has been studied by R. M. Wilder and D. L. Wilbur.

Hyperfunctioning tumors of the adrenal medulla cause either continuous hypertension or attacks of paroxysmal hypertension, probably as the result of an overproduction of epinephrine. These attacks are frequently associated with signs of instability of the sympathetic nervous system, such as tachycardia, emotional stability, vasoconstriction followed by vasodilatation and other like phenomena.

Tumors of the medullary portion of the adrenal glands are likely to be *paragangliomas* and are usually benign in character. C. H. Mayo, M. F. Porter and M. F. Porter, Jr., and A. M. Shipley have reported cases of adrenal paragangliomas which were operated upon with consequent relief of the syndrome of paroxysmal hypertension.

The *diagnosis* of hyperfunctioning medullary adrenal neoplasm is often difficult. The patient must be observed during an actual attack of the paroxysms of hypertension, since the blood-pressure may be normal during the interim. Bauer and Leriche emphasized the diagnostic importance of the parallel ascent of the curves of blood-pressure and blood sugar.

**AMENORRHEA.—Treatment.**—M. B. Goldberg and H. Lissner (Endocrinology 19:649 (Nov.-Dec.) 1935) treated a group of 8 patients whose principal complaint was amenorrhea with **emmenin** liquid (Collip). Menstruation had not occurred in this group of women for periods ranging from 3 months to 6 years. The ages of the patients ranged from 17 to 40 years. Four patients were not improved, in 1

the result was doubtful, while in 3 of the cases regular menses were re-established. Nine patients with *oligomenorrhea* were treated with estrogenic substance (**emmenin**). Of these, 3 were completely relieved, 5 definitely improved, and in only 1 was the result doubtful. A group of 7 patients who had irregular periods was also treated with emmenin. Of these, 4 were improved, and 3 became perfectly normal.

Kaufmann finds *primary amenorrhea* very difficult to influence. No permanent results, as a rule have been obtained by hormonal therapy. The outlook is much more promising in *secondary amenorrhea*. Once the menstrual periodicity is restored, the menses may continue regularly and spontaneously and in some cases pregnancy may occur. The treatment of *oligomenorrhea* with physiological doses of *follicular hormone* is most promising.

Low-dosage **irradiation of the pituitary gland and ovaries** is a very important adjuvant in the treatment of functional disorders of menstruation. It is of special value in *amenorrhea*, *oligomenorrhea* and *uterine hemorrhage* in the young woman. The value of x-ray therapy in restoring menstrual periodicity was emphasized in the report of C. Mazer and L. Spitz, Jr. (Am. J. Obst. and Gynec. 30:214 (Aug.) 1935). Twenty-three of 47 patients suffering from severe amenorrhea have been menstruating regularly, without the stimulus of incidental pregnancies for periods averaging 2 to 3 years following low-dosage x-ray treatment of the ovaries and hypophysis. Eight of 15 women complaining of *oligomenorrhea* likewise were restored to normalcy by low-dosage irradiation of the pituitary and ovaries.

The dose of x-ray exposure employed is equivalent to  $7\frac{1}{2}$  to  $12\frac{1}{2}$  per cent.

skin erythema dose or 50 to 80 roentgen units.

## SECONDARY AMENORRHEA.

—**Treatment.**—Before instituting treatment for secondary amenorrhea, attempts should be made to determine the primary gland at fault. The most important factor to be ascertained is the degree of ovarian function present in a given case. This may be determined by the history of the patient, diagnostic curettage, and by hormonal extraction of the blood and urine.

Since 1933, 25 cases of functional amenorrhea were observed at the Gynecological Endocrine Clinic of Lebanon Hospital, New York City. This group was studied and reported upon recently by A. B. Tames (Am. J. Obst. and Gynec. 32:845 (Nov.) 1936). With few exceptions, these women had received one or more unsuccessful courses of treatment prior to registration at the Clinic including the use of pills, hypodermic medication of ovarian and pituitary sex hormones and x-ray therapy of the pituitary and the ovaries. As a whole, these patients typified the more severe forms of secondary amenorrhea. Their ages ranged from 17 to 36 years, the average being 25 years. All of the patients had menstruated prior to the onset of the amenorrhea. Eighteen patients complained of absent menstruation for periods of 6 months to 3 years. Seven patients were amenorrheic for less than 6, but more than 3 months.

Each case was studied to exclude nonfunctional causes of amenorrhea arising from pathologic states of the genital organs, from nutritional disorders, or from tuberculosis. A basal metabolism and an analysis of the urine for gonadotropic and estrogenic hormones were then performed. The clinical and laboratory data were then analyzed for etiologic leads upon which to base the treatment. Menstruation was

restored, and the regularity of the menstrual cycles greatly improved in 60 per cent. of the patients.

The demonstration of a "premenstrual" or "secretory" type of endometrium by curettement not only indicates ovarian function, but also demonstrates a proper balance in the elaboration of follicular and luteal hormones. In addition, the finding of a high grade genital atrophy, in the form of ill-defined labia, conical and narrow vagina, and small uterus, also offers an index of the ovarian function.

**Desiccated thyroid extract** and **x-ray "stimulation" of the ovaries** proved to be the best agents in restoring menstruation in Tames' series of cases. **Thyroid extract** is not always well tolerated, even in small doses. The patients must be frequently reexamined for signs of thyroid intoxication, and the basal metabolic rate rechecked. The dose employed was the largest dose tolerated by the patient without producing toxic symptoms. As a rule, it ranged between 3 and 6 grains (0.2 to 0.4 Gm.) of thyroid extract (Armour) daily.

**Amniotin** and **follutein** were administered to 6 patients, all of whom were demonstrated to have poor ovarian follicular activity. Menstruation was reestablished with greater regularity in 2 cases.

**DYSMENORRHEA.—Treatment.**—In certain cases of dysmenorrhea the pain is produced by violent contractions of an irritable uterus. It has been proved experimentally in rabbits that corpus luteum extract (progesterone) will relax the contractions of the uterus (S. R. M. Reynolds). In dysmenorrhea of this type, relief is possible with injections of **progesterone**.

C. A. Elden and K. M. Wilson (Am. J. Obst. and Gynec. 32:91 (July) 1936)

noted that 8 (47 per cent.) of a group of 17 patients with functional dysmenorrhea obtained complete relief with doses of progesterone varying from  $\frac{1}{2}$  to  $\frac{6}{25}$  rabbit units. Two of the patients (11.7 per cent.) claimed only partial relief, and did not get total relief with larger doses of the hormone.

The remaining 7, or 41.3 per cent., of the patients did not receive any benefit from this therapy. No delay in the onset of the menstrual cycle was caused by the small doses of progesterone, and apparently no change was produced in the duration or character of the menstrual flow. The patients relieved by the hormone also had some relief of constitutional symptoms and only partial relief of the pain. Two patients not relieved by progesterone or any other known remedy, subsequently had **presacral sympathectomies** with complete relief.

The doses employed by Elden varied from  $\frac{1}{2}$  to 1 rabbit unit, given in single or divided doses, 3 to 6 days before the onset of the menstrual flow.

**Emmenin** (Collip) was employed in the treatment of 40 cases of functional dysmenorrhea by M. B. Goldberg and H. Lissner (Endocrinology 19:649 (Nov.-Dec.) 1935). In this group of patients all complained of pain which was severe enough to compel the majority of them to be confined to bed. Emmenin failed utterly in 8 cases; was of doubtful value in 7; produced definite improvement in 12; and achieved brilliant results in 13 cases. About 60 per cent. of the 40 patients were either entirely relieved or markedly improved.

**EXOPHTHALMIC GOITER.—Treatment.**—The value of iodine as a routine **preoperative** medication in exophthalmic goiter has been pointed out recently by J. L. De Courcy (Arch. Surg. 32:346 (Feb.) 1936), who has

noted a steady improvement in postoperative results and a lowering of mortality as a result of this preoperative treatment. This clinician employs large doses of aqueous solution of iodine—sometimes as high as 10 minims (0.6 c.c.) 3 times a day—and the results obtained fully justify him in continuing this course. In clinical work he has found that a period of iodine treatment of 10 days to 2 weeks is usually sufficient for patients whose glands are only moderately enlarged. In patients with the large hyperplastic type of gland, he looks for local changes in the thyroid itself and observes their relation to the abatement, or failure to abate, of the characteristic symptoms. In cases of this general type it is sometimes deemed wise to give iodine for as long as 4 weeks before considering the patient sufficiently prepared for operation.

De Courcy continues the administration of iodine after the gland has been removed, giving 31 grains (2 Gm.) of sodium iodine intravenously while the patient is on the operating table. During the first 24 hours after operation, about 100 minims (6.2 c.c.) is administered by rectum. If the patient is admitted to the hospital 4 or 5 days prior to operation, he keeps her in bed and administers 15 minims (1 c.c.) of iodine 3 times a day. In most cases the operation is performed at one session, but if the goiter is exceptionally large, he performs a **unilateral lobectomy**, and removes the second lobe about 3 days later, closing the wound entirely in the interval between the steps of the procedure.

**Subtotal resection** is most satisfactory in those patients who give definite evidence of thyroid hyperplasia with hyperthyroidism, together with congestive heart failure or angina pectoris. In this type of patient he has had particularly good results and has been able

to confer substantial benefit, equal to that following total excision, without subjecting the patient to any of the risks of the more radical procedure.

#### **HEMOPHILIA.**—*Treatment.*—

Various hormonal preparations have been employed lately to combat the blood dyscrasia known as hemophilia. Although the earlier reports of C. L. Birch, A. G. Foord and B. R. Dysart, H. T. Kimm and C. M. Van Allen, and others tended to show that the coagulation time was lessened and that an improvement in the clinical condition of patients with hemophilia occurred following ovarian principles and various preparations of female sex hormones, later reports indicate the failure of improvement with this type of therapy. Preliminary studies by R. P. Stetson, C. E. Forkner, W. B. Chew and M. L. Rich of observations on 7 patients with hemophilia treated by oral and parental administrations of various ovarian and estrogenic substances show that no improvement resulted in the coagulation of the blood or in the clinical state. Likewise, R. L. Brown and F. Albright noted no beneficial effect in one patient with hemophilia who received injections of large amounts of estrogenic substance over a 3-day period. Negative observations on the coagulation time and clinical condition of a hemophilic patient who received intramuscular injections of whole ovarian extract daily for 3 weeks, followed by the daily intramuscular injection of estrogenic substance for 2 weeks, were also made by J. Brem and J. S. Leopold.

Later, W. B. Chew, R. P. Stetson, G. V. Smith and O. W. Smith studied 2 patients with hemophilia for 10 and 13 months, respectively, while receiving no specific therapy and also while receiving preparations of estrogenic substance by mouth and subcutaneously,

corpus luteum intramuscularly, and the gonad-stimulating hormone from the urine of pregnant women subcutaneously. One patient also received stimulating doses of x-rays over the pituitary region. The administration of such hormones to these patients with hemophilia was not associated with a demonstrable improvement in the clinical condition or with a significant diminution in the coagulation time of the blood. The urine from untreated patients with hemophilia usually contained a larger amount of estrogenic substance than did the urine from normal males of comparable age.

As a result of their observations, Chew and his associates (*loc. cit.*) feel confident that persons with hemophilia have no lack of estrogenic principle in their urine and, although it does not necessarily follow, probably have no deficiency of this substance in their blood. They have been unable to alter the characteristic fluctuations of the prolonged coagulation time of the blood in hemophilia by the administration of estrogenic substances.

**HYPERINSULINISM.**---In 1924, S. J. Harris first reported his observations on hyperinsulinism. Since this report, many articles have been published describing cases of hyperinsulinism due to various pathologic processes in the islands of Langerhans. In 1929, Graham (cited by M. Corff (*Am. J. Surg.* 34: 241 (Nov.) 1936) reported the first definite cure of a case of hyperinsulinism by **excision of a tumor of the pancreas** from a patient who had had attacks of unconsciousness, etc., for several years. Before operation the blood sugar was 40 mg. The tumor was 1.5 cm. in diameter, located in the middle of the body of the pancreas and identified as an adenoma of the islands of Langerhans.

**Types.** M. Corff (*loc. cit.*) states that there are 2 types of hyperinsulinism: the *true hyperinsulinism*, in which there is an excess of insulin sent in to the circulation, due to alterations in the islands of Langerhans; and the *relative hyperinsulinism*, in which an excess of insulin enters the circulation due to the removal of factors which normally inhibit insulin secretion, the islands of Langerhans being normal.

**Etiology.** Hyperinsulinism is most often encountered in the treatment of diabetes as a result of overdosage of insulin. True hyperinsulinism may be caused by tumors or hypertrophy of the islands of Langerhans. Relative hyperinsulinism may be induced by a lack of antagonistic glandular action, as in hypothyroidism or in diseases or tumors of the adrenal gland. In hypothyroidism, a low blood sugar is often found, since the antagonistic action of thyroid secretion is missing. In myxedema, the average blood sugar is 80 mg.; in more severe cases it is correspondingly lower. Again, in Addison's disease there is an associated hypoglycemia.

Hypoglycemia is also encountered in cases of pituitary tumor and pituitary deficiency, and in other diseased processes of the base of the brain. Corff claims that most cases of relative hyperinsulinism are due to pituitary disturbances, usually hypopituitarism, and the next largest amount of cases are due to hypothyroidism.

**Symptoms.**---The symptoms are those of hypoglycemia, *i. e.*, tremors, nervousness, weakness, sweating, excessive pallor, a feeling of hunger, anxiety and emotional instability. As the case becomes more severe, there develops mental confusion, amnesia, epileptiform convulsions, sensory and motor aphasias, delirium, coma, collapse and, finally, death.



The most characteristic laboratory finding is a fasting blood sugar of 40 to 60 mg. Another characteristic test is with adrenalin. In a normal individual an injection of 1 c.c. of 1:1000 adrenalin raises the blood sugar an average of 30 to 40 mg. in 30 minutes and the curve gradually returns to normal in about 1 hour. The rise is due to a stimulation of glycogenolysis in the liver and can only take place if the liver is normal.

**Treatment.**—In the treatment of the acute attack of hyperinsulinism, an intravenous injection of **glucose** will bring the patient from stupor or coma to an absolutely clear mental state. If no glucose is at hand, the injection of 1 c.c. (16 minims) of **adrenalin** (1:1000) or 1 c.c. (16 minims) of **pituitary extract** will also give quick relief. If these preparations are not available, the feeding of some quickly absorbed glucose such as **sugar, candy,** or **orange juice** will often alleviate the symptoms.

For the *chronic* case, in which no endocrine disturbance can be found, Seale Harris advises for the average person of 150 pounds, a diet of 2250 calories per day in frequent meals of 5 to 7 a day. A diet of 90 to 120 grams (3 to 4 ounces) carbohydrates, 60 to 70 grams (2 to 2½ ounces) protein, and the rest in fats may be used. If hypothyroidism is present, small doses of **thyroid extract** (¼ to 4 grains — 0.016 to 0.26 Gm. — daily) should be administered.

Surgery is indicated for those cases which no longer respond to medical measures. **Enucleation** of an **adenoma** has brought cure in certain cases. In those cases in which no tumor is palpable, clinical cure can follow the partial or subtotal **resection of the pancreas.**

The milder cases can be freed of symptoms for long periods of time by

**dietary measures.** In operative cases, **removal** of a single **adenoma** may bring about a complete cure. In those cases in which no definite tumor is found, the prognosis depends on the amount of pancreatic tissue removed at operation. If adequate tissue is removed a permanent clinical cure may be expected.

### **HYPERPARATHYROIDISM.**—

This condition is usually due to an actively functioning adenoma of the parathyroid glands, although cases have been reported in which all the parathyroid tissue was found to be hyperplastic.

W. Bauer ably describes the normal and the pathological aspect of the parathyroids.

The chief function of the parathyroid glands is the regulation of calcium and phosphorus metabolism. The bones are the only storehouse of calcium in the body. They are composed mainly of a complex calcium salt, containing calcium phosphate and carbonate ions. Normally, the serum calcium varies from 9.5 to 11 mg., and the serum inorganic phosphorus from 3.5 to 4.5 mg., per 100 c.c. The relative state of constancy thus maintained is proof in itself that the bones are labile structures. The calcium and phosphorus are absorbed from the bones in time of need, and in time of excess are deposited in the bones. The bone trabeculae serve as the most readily available depot, and the cortex being the first spared in the process of mobilization. The blood gives up calcium and phosphorus to the bones when present in excessive amounts. The action of the enzyme phosphatase brings about the state of supersaturation of the blood, with consequent deposition of calcium and phosphorus in the bone.

Calcium and phosphorus entering into the system are dependent upon their absorption from the gastrointestinal tract,

the amount absorbed depending on: (1) the composition of the diet; (2) the acidity of the gastrointestinal tract; (3) the intestinal rate; (4) digestion and absorption of fat; and (5) the supply of vitamin D.

The diet and the supply of vitamin D are probably the most important of the factors involved. Should any of these factors be at fault for any considerable length of time, gastrointestinal absorption of calcium and phosphorus is interfered with, resulting in a negative calcium and phosphorus balance. Rickets and osteomalacia owe their origin to this disturbance.

Normally, calcium and phosphorus are lost from the body by way of the gastrointestinal tract and kidneys. Fecal calcium consists of both the unabsorbed dietary surplus, and that which has been reëxcreted into the bowel, the diet being normal at this time. Atrophy of disuse and osteitis deformans at times cause increased excretion by these avenues. The increase is slight in comparison with that occurring in acidosis, hyperthyroidism and hyperparathyroidism. Should the increased excretion exceed the intake, a negative balance results and the latter, if persistent, results in marked generalized decalcification.

**Symptoms.**—Hyperparathyroidism, irrespective of the causative factors, is characterized by paresthesias, muscular pains and cramps, carpopedal spasm, laryngismus, and loss of consciousness. Laboratory tests will disclose a low serum calcium and a high serum phosphorus. A positive Chvostek and Trousseau sign usually may be elicited, as well as evidence of increased excitability of nerves (Erb's sign).

Clinically, hyperparathyroidism may manifest itself in the following forms: (1) von Recklinghausen's disease or generalized ostitis cystica, (2) osteoporosis, (3) nephrolithiasis, (4) acute

parathyroid poisoning, and (5) a condition complicated by or simulating Paget's disease. Increasing the production of parathyroid hormone will produce characteristic changes in calcium and phosphorus metabolism. Observations show that in a normal individual, the administration of an active parathyroid extract will result in an elevated serum calcium, a low serum phosphorus, an elevated serum phosphatase, and an increased calcium and phosphorus excretion. Generalized rapid decalcification caused by the increased excretion of calcium and phosphorus produces the most pronounced changes in the long bones, spine, sacrum, pelvis, skull, jaw and flat bones of the thorax. The bones showing the least transformation are the phalanges, the tarsals, and the short tubular bones.

It has been found that hypercalcemia and hyperphosphaturia are often responsible for the formation of renal calculi. The other types of renal complications are as follows: (1) pyelonephritis secondary to calcium phosphate stones; (2) calcium deposits in kidneys as well as other organs in acute parathyroid poisoning; (3) pyelonephritis secondary to calcium phosphate stones.

**Diagnosis.**—In hyperparathyroidism there is no single sign that is diagnostic of this condition. The signs may be classified in 3 groups as follows: hypercalcemia, skeletal changes, and increased excretion of calcium and phosphorus. The symptoms consist of anorexia, nausea, vomiting, abdominal pain, constipation, lassitude, weakness, and loss of weight. Hypotonia is also common. Skeletal changes are dependent upon the duration and the severity of the condition. Some other common symptoms are: a waddling gait, bone pain, spontaneous fractures, bone tumors, kyphosis and loss of height. Polyuria and polydipsia are symptoms chiefly referable to

hypercalcinuria and hyperphosphaturia. These symptoms may be so marked as to suggest diabetes insipidus. Enuresis and nocturia are not uncommon symptoms. The passage of gravel or small stones may cause pain on urination. In some of the reported cases, renal colic was the first and only symptom. In this particular group, no bone changes may be demonstrable on x-ray examination.

**Differential Diagnosis.**—The differential diagnosis, in the final analysis, depends not so much on the symptoms, as on the laboratory studies. In most cases, laboratory reports of the serum findings are sufficient.

It is rare that a bony biopsy is ever required. The skeletal diseases that are most often confused with hyperparathyroidism are, osteomalacia, osteoporosis due to senility, hyperthyroidism, disuse or inactivity, a basophilic adenoma of the pituitary or a tumor of the suprarenal cortex, Paget's disease, solitary bone cysts, solitary benign giant-cell tumor, osteogenesis imperfecta, multiple myeloma, metastatic malignancy, Schüller-Christian disease, Gaucher's disease, erythroblastic anemia, and radium poisoning.

Since 1915, when Schlagenhauser and Maresch (cited by F. Mandl: Beitr. z. klin. chir. 162:643, 1935) first proposed removal of an enlarged parathyroid in a case of Recklinghausen's generalized osteitis fibrosa, over 100 cases have been operated. Mandl states that in typical cases and in the great majority of cases the calcium metabolism quickly returns to normal, and the decalcified bones become more solid. The most important chemical findings of Recklinghausen's osteitis fibrosa are hypercalcemia and hypophosphatemia.

The difference between Recklinghausen's disease and Paget's disease is proved definitely by: (1) the absence of hypercalcemia in the latter; (2) the

fact that never has a parathyroid tumor been found in Paget's disease of the bones; (3) the pronounced decrease in the excretion of calcium in the urine in this condition. However, it is Mandl's belief that Paget's disease is related in some manner to the parathyroids.

**Treatment.**—In a recent article, J. Hellstrom (Nord. med. tidskr 9:331 (Mar. 2) and 9:375 (Mar. 9) 1935) states that the operative mortality in the cases of parathyroidectomy reported up to date is about 10 per cent. In 1 of every 5 cases of hyperparathyroidism the disease is due, according to O. Cope (New England J. Med. 213:470 (Sept. 5) 1935), not to a single adenoma or multiple adenomas, but to a diffuse hyperplasia of all parathyroid bodies. The treatment in these cases is **subtotal parathyroidectomy**. The main difficulty lies in determining the amount of tissue to remove. Removal of insufficient tissue may result in only temporary relief, while the removal of too much tissue may cause tetany.

Three cases of *generalized osteitis fibrosa cystica* were reported by D. P. Cuthbertson and W. A. Mackey (Glasgow M. J. 123:249 (May) 1935). The first case was in a woman, 53 years of age, who was operated upon for a *parathyroid adenoma* and died of tetany 33 days later. In the second case, a woman of 40 years of age was operated upon in two stages. She died of hypostatic pneumonia a year and four months after the second operation. In the third case, a parathyroid adenoma was removed from a girl 19 years of age who later made considerable improvement.

Patients in whom parathyroid adenomas have been successfully removed showed extraordinary improvement if the tumors were removed early in the disease. In the advanced cases, the disease can be arrested, but the patient will

be left more or less of an invalid. It is necessary, therefore, to diagnose the case early and apply the required operative treatment.

Three methods of treatment are employed for hyperparathyroidism, *i. e.*, surgical, medical and x-ray. O. Cope (*loc. cit.*) states that medical management is very dangerous. Irradiation of the glands thus far has not given conclusive results. The surgical treatment of hyperparathyroidism is not similar to thyroid surgery, in that replacement therapy is not satisfactory in postoperative tetany.

### HYPERTRICHOSIS.—*Etiology.*

—Disturbances in the distribution and growth of hair in the female are encountered in several types of endocrinopathies. They are met with in patients with hyperfunction or hypofunction of the pituitary, thyroid, ovary or adrenal glands. Yet, in many individuals with generalized hypertrichosis, no evidences of endocrine disorder can be detected. Further, in many patients with definite endocrine imbalance the distribution and growth of hair may be entirely normal.

In a recent article, H. D. Niles (*Arch. Dermat. and Syph.* 32:580 (Oct.) 1935) reported on 31 patients with hypertrichosis. In 22 cases the hypertrichosis was generalized; in 3 only the face, arms and legs were affected; in 2 only the face; and in 4 the location was not recorded. In 16 patients, menstruation was regular, and in 6 it was irregular. Acne was present in 6 cases.

Niles assumes the presence of adrenal hyperactivity as the basis for the hypertrichosis. Associated with hirsutism of adrenal origin there are regression of the breasts, deep voice, loss of libido, hypertrophy of the clitoris and obesity. According to M. A. Goldzieher, "hirsutism is a definitely adrenal syndrome, as in

all the cases observed so far there was either a tumor or a distinct hyperplasia of the adrenal cortex." In agreement, Z. K. Cooper avers that there is much evidence that disturbed functions of the adrenals results in disturbed growth of hair.

**Treatment.**—Inhibitory doses of **x-rays** have been employed to combat the abnormal growth of hair in the female. Niles employed a single maximal dose of 350 to 400 R units, using 200 K. V. filtered with 0.5 to 0.75 mm. of copper at a target distance of 40 to 56 cm. to each adrenal gland (<sup>2</sup><sub>3</sub> S. E. D.) once a month. A roentgenogram of the position of the kidneys was taken prior to starting treatment so as to determine as accurately as possible the proper site of irradiation.

Twelve patients were treated with 1 to 9 treatments at various intervals. As the dose mentioned, given at intervals of 1 or 2 months, proved ineffective, a dose of one-third S. E. D. was given 3 times a week. In none of the patients was a definite loss of hair noted. None noticed any falling of hair from the face, and in none were the hairs on the face loosened. In several cases new hairs continued to appear, but in others no new hairs appeared after the institution of the x-ray therapy. Niles concludes that x-ray therapy in the doses administered apparently had no effect, either good or bad.

Since hypertrichosis is only a manifestation of pronounced disorders in endocrine glands, such as the pituitary or adrenals, alleviation can only be expected if the **primary cause** can be **removed**. Cases are on record where there was a complete return to normal hair growth after the removal of portions of hyperplastic adrenal glands or cortical adenomas. Attention to this phase of the subject is called elsewhere.

## MENOPAUSE, DISORDERS OF.—*Etiology.*—

The disturbances of the climacterium ("critical" age or menopause) are due, for the most part, to the gradual decline of ovarian function, as evinced by the abrupt appearance of the symptoms, sometimes within a day or two, after surgical or x-ray castration. The prompt relief of these symptoms in many of these patients by the administration of potent ovarian extracts strongly supports this view. Maroñon, however, believes that the menopausal symptoms are due to antecedent structural and functional changes in the thyroid, adrenal, and pituitary glands, and that the ovarian changes are secondary and not causative. The hypertension, hemicrania, palpitation and flushing of the face are most likely due to vasomotor irritability as a result of hyperfunctional reaction of the adrenals and of the thyroid.

**Treatment.**—The use of potent preparations of ovarian extract (follicular hormone, estrin, theelin, progynon, etc.) is of great value in alleviating the disturbances and distressing symptoms of the menopause and stabilizing the vasomotor nervous mechanism. **Estrogenic substances** have been used by E. Novak, Catharine MacFarlane (Am. J. Obst. and Gynec. 31:663 (Apr.) 1936), M. B. Goldberg and H. Lisser (Endocrinology 19:649 (Nov.-Dec.) 1935), and others in the treatment of the menopause with good results. Novak reported his observations in following the course of treatment of 95 women suffering from menopausal disturbances which indicated that the continued use of adequate amounts of estrogenic substance tends to shorten the course of the condition. In no case was therapy required for a period longer than 30 months. The choice of commercial preparation used may be made on a basis

of cost, provided a biologically standardized preparation is employed.

MacFarlane (*loc. cit.*) employed **emmenin liquid** (Collip), an alcohol soluble, ether insoluble complex present in acetone extracts of human placenta, in the treatment of 18 women complaining of the vasomotor disturbances of the menopause. Ten of these women were improved; 8 very definitely, and 2 rather indefinitely.

M. B. Goldberg (*loc. cit.*) treated 8 patients, varying in age from 27 to 55 years, for menopausal complaints (3 of whom had artificial menopause) with **emmenin** (Collip). In 2 the results were doubtful; 4 patients were improved; and 2 were completely relieved.

Emmenin is administered by mouth, 1 teaspoonful in water or orange juice 3 times a day. This dose may be increased to 6 teaspoonfuls a day for 1 week to 10 days. One teaspoonful represents about 25 Gm. (6¼ drams) of placental tissue.

Estrogenic substance in the form of **hydroxyestrin benzoate, dihydroxyestrin (theelin, progynon B)** is very useful in relieving menopausal disturbances. A dose of 2000 rat units of progynon B will usually relieve the vasomotor disturbances of menopausal women for a period ranging from 1 to 2 weeks.

For the relief of severe menopausal symptoms in cases where follicular hormone has failed to bring about a beneficial result, **irradiation of the pituitary gland** has been recommended by C. G. Collins, E. P. Thomas and L. J. Menville (Am. J. Obst. and Gynec. 31:115 (Jan.) 1936), who treated 33 patients at the Hutchinson Memorial Clinic, New Orleans, La., by this method.

The irradiation dose for each exposure was 148 r with these factors: 12 in. D., 5 ma., 120 K. V. P., 1 mm.

A1. and 0.25 cu., 8 min. The total dosage for each series was 296 r. The first treatment is given through the right temporal region and on the following day is repeated on the left side. After an interval of about 3 weeks, the same procedure is again performed, making a total series of 4 exposures, with a total dosage of 529 r to the skin surface.

The patients treated complained severely of the menopausal symptoms and had sought relief from various sources without success. Each case had previously been treated with sedatives such as luminal and bromides, and several had received injections of follicular hormone. The results were so striking in the first few cases treated in this manner that this therapy has been continued and is employed in all women suffering from menopausal symptoms who experienced no alleviation from the use of sedatives.

Following pituitary irradiation, the flushes, sweats, and headaches have diminished in severity and in frequency of occurrence to the point where they are no longer annoying, and, in a number of cases, have entirely ceased. The nervousness has markedly improved and pains and stiffness in the joints accompanying the menopause have been relieved.

Improvement is most often noted during the third week of treatment and all patients, except two, have obtained complete relief by the end of 3 weeks from the last exposure.

The dosage of x-rays used in the treatment of menopause is a destructive one in Collins' belief, and causes a decrease in the concentration of prolan in that manner. The use of deep x-ray therapy is based on the finding that in the menopausal syndrome there is an overactivity of the anterior lobe of the pituitary gland which may be the primary cause

of the symptoms. An attempt will subsequently be made by Collins to demonstrate the fact that the relief of symptoms afforded by irradiation is accompanied by the disappearance of excess prolan and that this is the effect of a destructive dose of x rays to the hypertrophied pituitary gland.

#### MIGRAINE. — *Treatment.* —

Hormonal studies to determine the endocrine basis underlying the condition of migraine were recently made by S. J. Glass (*Endocrinology* 20:333 (May) 1936). The relationship of prolan A and estrin was studied in 10 young and migrainous women with ovarian dysfunction. Quantitative hormone assays showed a reversal of the normal ratio in the direction of increased prolan A and decreased estrin output. **Estrogenic therapy** tended to correct the hormonal imbalance by suppression of the prolan A secretion with concomitant relief of the symptoms of migraine in 80 per cent. of cases. Prolan administration resulted either in no relief or intensification of the headache.

At this point it may be mentioned incidentally that the REVIEWER has found hypodermic injection of **ergotamine tartrate** (**gynergen**, Sandoz) will in practically every case relieve within an hour or two a progressive case of acute migraine. Its action is on the sympathetic nerve fibers.

#### MYXEDEMA. — *Diagnosis.* —

Cases of well-developed myxedema should be recognized without difficulty. However, the type of case which makes diagnosis difficult is the one in which the patient suffers from a moderate degree of hypothyroidism without any definite evidence of thickened skin or fluid retention. The majority of patients with deficient thyroid function have more or less constantly a slow pulse and a sub-

normal temperature. C. H. Davis (Am. J. Obst. and Gynec. 30:570 (Oct.) 1935) has observed that practically all individuals who have slow pulse and subnormal temperature have a low basal metabolic rate. There is also another group of patients who may manifest an elevated pulse and normal temperature, with a lessened basal metabolic rate. **Thyroid therapy** brings about a marked improvement in their physical condition.

**Complications.**—In myxedema not complicated by a psychosis there is a specific mental condition characterized essentially by psychomotor retardation and fatigability, according to A. J. E. Akelaitis (J. Nerv. and Ment. Dis. 83:22 (Jan.) 1936). The patients are likely to be depressed and irritable, depending on the degree of myxedema and the type of individual. The most frequent type of *psychosis* met with in myxedema is a dysergastic (delirious; hallucinatory) reaction characterized by a clouding of consciousness, which may progress to complete disorientation, vivid hallucinations that are not primarily complex, determined unsystemized delusions of persecution and excitability. Under treatment with **thyroid** a definite improvement occurs. It is advisable to commence with small doses of thyroid, because these patients are extremely sensitive to the extract.

**Treatment.**—**Thyrotropic hormone** has been employed in the treatment of such conditions as *myxedema*, *cretinism* and *obesity*. A report of the use of this hormone in the treatment of a man, aged 45, in whom the myxedematous condition had developed gradually over a period of 4 or 5 years, was made by A. Schneiderbauer (Med. Klin. 31:1500 (Nov. 15) 1935). This patient was given daily intramuscular injections of 600 units of the **thyrotropic hormone of the anterior pituitary lobe**. The first series of treatment lasted 15 days, in

the course of which 9000 units were administered. As a result of the therapy, the basal metabolic rate changed from minus 30 per cent. to plus 14 per cent.; the pulse rate increased; there was a reduction in the body weight; and a definite change in the psychic behavior occurred. The fatigue disappeared and the patient became alert and industrious. When the treatment was discontinued for several weeks, the basal metabolic rate and the iodine content of the blood again decreased, and there was once more an increase in weight. The series of injections was repeated twice, in order to bring about improvement in the condition.

#### OVARIAN DYSFUNCTION.—

Disturbances of the normal secretion of the ovaries are manifested in the genital tract in two chief disturbances, *e. g.*, amenorrhea and uterine bleeding. *Amenorrhea* may be primary or secondary. Primary amenorrhea may be associated with hypoplastic genitalia or with well-developed sexual organs. *Uterine hemorrhage* may occur as a result of persistent follicle formation and a continuance of estrin secretion with a lack of corpus luteum function.

C. Kaufmann (J. Obst. and Gynaec. Brit. Emp. 42:409 (June) 1935), in order to produce the pregravid changes in the endometrium of the castrated woman, found it necessary to administer first the **follicular hormone**, which brings about the proliferative phase of the uterine mucous membrane, and then the **corpus luteum hormone**, which converts the proliferated endometrium into the secretory phase. He concludes that in severe endocrine disturbances of the ovaries the doses of the follicular hormone previously employed were inadequate and therefore useless. It is now known that the dose necessary for adequate proliferation of the endometri-

um in a castrated woman is not less than 1,000,000 international units.

The pathological exaggeration of the proliferation phase, the so-called cystic hyperplasia of the endometrium, gives rise to *functional metrorrhagia*. Since the excessive production of follicular hormone is associated with deficient corpus luteum formation, substitution therapy with **corpus luteum hormone** is employed. While large quantities of corpus luteum hormone (up to 90 rabbit units) are required to convert an abnormally proliferative phase of the endometrium into the premenstrual or secretory phase, much smaller doses (10 to 20 rabbit doses given over 5 or 6 consecutive days) will often cause the cessation of uterine bleeding.

#### PELVIC DISEASE.—*Treatment.*

—C. F. Fluhmann and P. E. Hoffman (West. J. Surg. 43:678 (Dec.) 1935) studied the effect of the use of estrogenic substance in 29 adults with acute and chronic pelvic inflammatory disease. The use of this substance was based on the assumption that estrogenic principles stimulate the defensive mechanism of the pelvic organs. **Amniotin** dissolved in oil was the preparation employed. It contained 500 or 1000 rat units per c.c. It was given intramuscularly in 0.5 or 1 c.c. (8 to 16 minims) doses daily, until the patient had received from 5 to 16 injections, and a total dosage varying from 3750 to 16,000 rat units. Twenty-four patients were ambulatory with *subacute* or *chronic salpingitis*, while 5 were in the hospital and febrile. Twenty-three patients exhibited definite palpable *adnexal masses* at the onset of the treatment. Several weeks after the course of treatment, reëxamination disclosed complete healing, with a disappearance of masses in 7 cases, while 9 showed definite improvement, but with palpable pathologic changes in the pelvis. Seven pa-

tients did not show improvement, and in 5 of these operation was necessary later. Of 27 patients, 9 claimed that they had obtained complete relief from *pelvic pain* within 2 to 6 weeks after injections were begun. Of 19 cases with *profuse vaginal discharge*, definite improvement took place within 2 to 6 weeks in 7 patients; whereas the amount of discharge was unaffected in 12 of the cases.

#### PITUITARY GLAND.—PITUITARY BASOPHILISM.\*

Pituitary basophilism is the term applied to the symptom-complex brought about by an invasion of the pituitary gland with basophilic cells. Harvey Cushing, in 1932, separated from the group of so-called polyglandular disturbances a definite syndrome and has shown from a study of autopsied cases that a basophil adenoma of the pituitary gland is the cause of this condition. Recently, however, the name of Cushing's disease or syndrome has been attached to other similar syndromes caused by adrenal hyperplasia or tumor. This has given rise to considerable confusion in this field. The use of the term *Cushing's syndrome* should be restricted to those cases where an adenoma of the pituitary is suspected or has been found at autopsy.

The important *symptoms* of pituitary basophilism include: obesity, especially of the face, trunk and abdomen; hirsutism with masculine distribution of hair; sexual disturbances (impotence in male, and amenorrhea in the female); cutaneous striae over the breasts and abdomen; decalcification of the bones; hyperglycemia; hypertension; polyuria; polydipsia, and various nervous manifestations. There is, in addition, a tendency to polycythemia. Headache may also be an accompaniment.

\* See also section on NEUROLOGY.



There is apparently a close, but not understood, relation between disturbances caused by overaction of the adrenal cortex and those resulting from pituitary adenoma of the basophilic type. In certain cases the presence of adrenal cortical neoplasm has been found at autopsy to have been associated with basophilic invasion of the pituitary gland.

I. H. Pardee outlined 5 syndromes of pituitary basophilism: The Cushing syndrome, a mixed syndrome of intrasellar pituitary disease; a syndrome in which the disturbances seem to point to involvement of the adrenal cortex; a prepubertal or pubertal basophilic syndrome, and the postmenopausal basophilic syndrome. Pardee believes that transitory or mild degrees of pituitary basophilism may exist not only in adolescents but in premenopausal and postmenopausal states.

W. G. MacCallum and his associates report a proved case of basophilic adenoma as follows:

The patient was a woman, aged 25 years. She complained of increased weight, change in her appearance, and amenorrhea. She noted the development of broad reddish-purple lines over her shoulders, chest and abdomen. There was edema of the ankles and legs. Later she developed polyphagia and polydipsia, and said that she would drink 2 gallons of water daily. There was also very marked polyuria.

X-rays of the bones showed evidence of demineralization. The blood count showed R. B. C. 6,050,000; W. B. C. 18,000; Hb. 114 per cent. Basal metabolic rate was minus 6.

The finding of osteoporosis of the vertebræ, as well as of the skull, the high red cell count and hemoglobin, the glycosuria, the obesity and cutaneous striæ, seemed convincing evidence that this was a case of *Cushing's syndrome*.

Gynecological examination of the patient revealed nothing, but in order to exclude the possible existence of an adrenal tumor, pyelograms were taken of the right kidney, which showed no abnormality of the pelvis.

Following this examination the patient developed a pyelitis and a generalized infection from which she succumbed.

Autopsy revealed a basophilic adenoma of the pituitary gland. The left adrenal weighed 14.75 grams and the right 18 grams. On numerous cross sections the tissue appeared normal except that the right adrenal showed a number of small abscesses scattered through its substance.

W. G. A. Swan and G. E. Stephenson likewise report a case of basophilic adenoma in a woman aged 30, who for 4 years had suffered from abdominal obesity, hirsutism and periods of amenorrhea. Death occurred suddenly during an attack of renal colic. Autopsy revealed the enlargement of the hypophysis and microscopically it was found that nearly the whole of the anterior lobe of the pituitary consisted of a basophilic adenoma.

Another case of basophil adenoma of the pituitary body found at autopsy was described by H. G. Close. Apart from the high blood-pressure, there was no reason to suspect either the syndrome or the pituitary lesion, and the finding of the basophil adenoma was purely accidental. The author states that if a large series of pituitary glands are studied, it will be found that the invasion of the posterior lobe by cells growing out from the pars intermedia is common, particularly in middle-aged individuals.

The *treatment* of basophilic adenoma of the pituitary gland is deep **x-ray irradiation**, to which eosinophilic and basophilic cells seem to react most favorably, according to C. W. Rand. Improvement was noted in a case of Cushing's syndrome after deep x-ray therapy by F. Jainen. In cases of pituitary basophilism not responding to irradiation, attention should be directed to the adrenal glands. X-ray examination of the renal regions should be made to determine the possible presence of adrenal neoplasm. As has been mentioned elsewhere, Crile has employed **resection of the nerves of the adrenal glands and partial adrenal-ectomy** in this type of case with a degree of success. According to W. Walters, cases of suprarenal cortical syndrome indicate that surgical exploration of the adrenal glands is advisable, unless definite evidence of a pituitary tumor is present.

On the assumption that the manifestations of Cushing's syndrome are due in a large part to adrenal hyperactivity, G. Crile, H. Turner and E. P. McCullagh (New York State J. M. 36:475 (Apr. 1) 1936) have performed **denervation of the adrenal glands** in four cases.

studies of the sella turcica showed no abnormality. Left adrenal denervation was performed and several months later operation was performed on the opposite side, at which time a partial adrenalectomy was done. Signs of adrenal insufficiency developed and were controlled by eschatin.

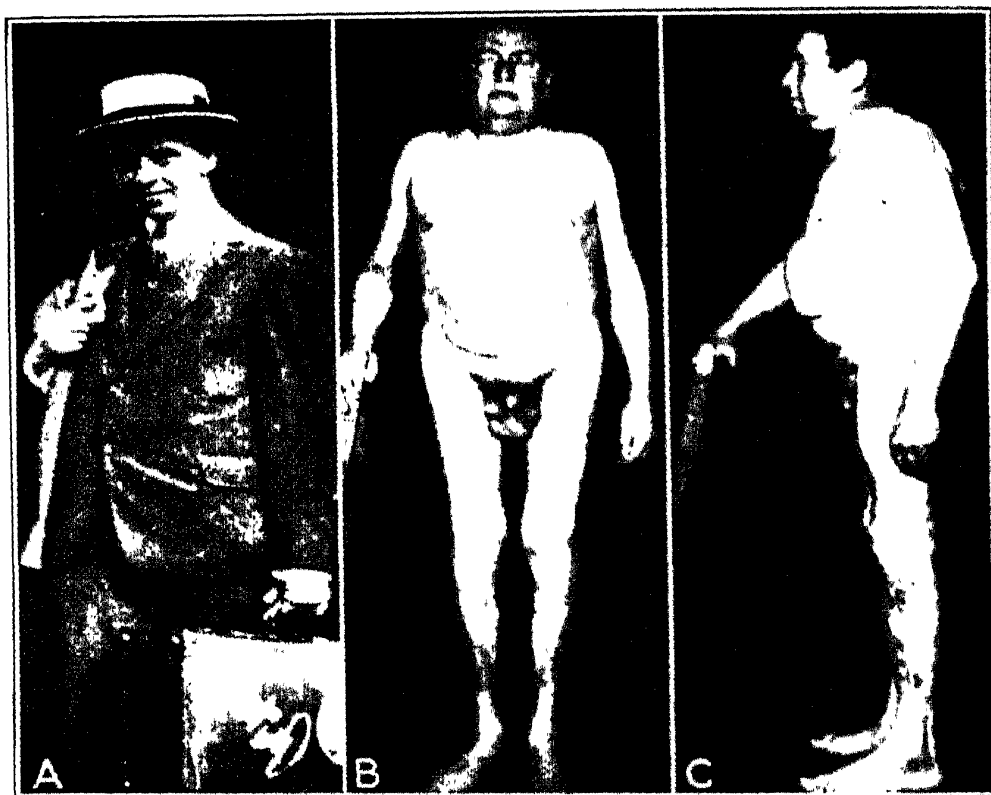


Fig. 1.—Photograph of patient. *A*, taken at age of 24; *B* and *C*, on admission to hospital. *B* shows spindling extremities and protuberant abdomen, and *C*, dorsal kyphosis and facial adiposity. (Lawrence and Zimmerman: Arch. Int. Med.)

They also denervated the adrenal glands and divided the major and minor splanchnic nerves on each side in 23 cases of polyglandular disease. In every case some if not all of the symptoms were alleviated after the operation.

One patient was a girl, aged 17 years, who complained of oligomenorrhea, hirsuties, enlargement of the breasts, headaches, and fatigue. She had gained 20 pounds in 2 months. She developed atrophic striæ on the breasts and thighs. The visual fields were normal. X-ray

Menstruation returned in 5 months and continued to be regular and normal in amount. Superfluous hair on the face, abdomen and extremities completely vanished. The skin became normal in color and texture. The patient improved remarkably until about 1½ years after the operation, when she became ill and died from acute epicarditis. Necropsy revealed a chromophobe adenoma of the pituitary gland, with possibly scattered basophilic cells. The adrenals showed a reduction of the cortical tissue and fibrosis.

Crile believes that the adrenal probably plays the major rôle in the adreno-genital syndrome because of the satisfactory results obtained by him and others in alleviating the symptoms by denervation or resection of the adrenals.

The exclusion of the hypophysis as the site of the lesion cannot always be made. This is exemplified by one of the cases

his admission, the patient had been well and had taken good care of himself. The following symptoms then made their appearance: increasing weakness, loss of libido, lumbago, dyspnea, nocturia, edema of the ankles, eruption in the skin of the nose, ecchymoses on the slightest injury, and kyphosis.

X-rays of the complete skeleton revealed marked and striking generalized decalcification. The patient had a decreased sugar tolerance.

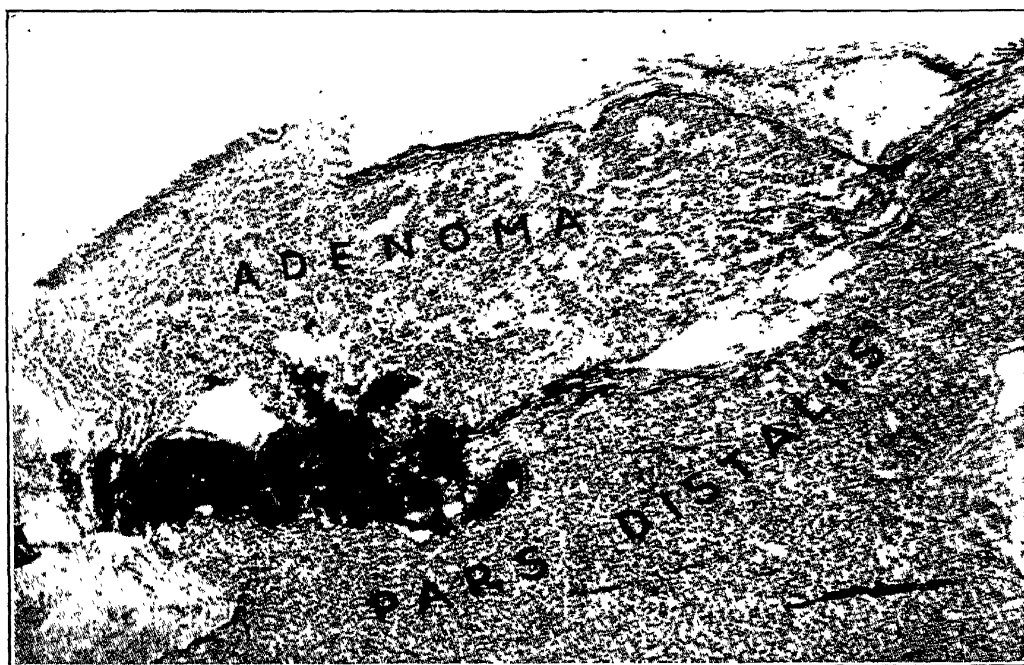


Fig. 2.—Basophilic adenoma beneath dura covering pars anterior of pituitary body with colloid at lower border of tumor on left side. Hematoxylin and eosin stain; X 30. (Lawrence and Zimmerman: Arch. Int. Med.)

reported by Walters, in which post-mortem examination, several months after operation, in which the adrenals were found to be normal in appearance, disclosed a basophilic adenoma of the pituitary.

A case of pituitary basophilism was reported by J. H. Lawrence and H. M. Zimmerman (Arch. Int. Med. 55:745 (May) 1935) in a male in which the condition was recognized during life and the diagnosis was confirmed by necropsy.

*Case Report.*—The patient was a man aged 44, who was admitted to the hospital because of severe pain in the chest, with the diagnosis of coronary occlusion. Until 4 years prior to

Postmortem examination revealed an inactive basophilic adenoma of the anterior pituitary gland, cortical hyperplasia and adenomas of the parathyroid bodies, and diffuse skeletal demineralization.

The basophilic adenoma in the anterior pituitary lobe, although 4 mm. in the greatest diameter, did not appear active on microscopic examination. Many of the cells were rather small and contained few granules. There was also an infiltration of basophilic cells in the neurohypophysis.

Another feature of unusual interest in this case was the presence of the small adenoma in one of the parathyroid glands. This condition had previously been observed in the case of C. G. Schmorl and Molineus.

**SIMMONDS' DISEASE (PITUITARY CACHEXIA).**\*—Pituitary cachexia, also known as Simmonds' disease and multiple ductless glandular sclerosis, is a specific endocrine syndrome in which profound cachexia is the most prominent symptom. Morris Simmonds originally described this syndrome in 1914, and since then sporadic cases have been reported in the literature. More than 50 cases were reported in the German literature from 1914 to 1933.

**Symptoms.**—The disease has an insidious onset, is progressive in course, and the outlook is grave, especially in untreated cases. Clinically, the condition is characterized by marked loss in weight, weakness, mental lethargy, premature senility, and sexual disturbances. There are, in addition, trophic skin changes, loss of pubic and axillary hair, low blood-pressure, and low basal metabolism. Emaciation is the most striking feature, and the loss of weight is more severe than that met with in other conditions. Amenorrhea may be the first sign encountered.

The basal metabolic rate is low in Simmonds' disease, and a reading of minus 25 to 23 per cent. is not unusual. Other symptoms and findings, such as disturbance in water balance, polyuria, polydipsia, headache, dizziness, dental caries, and hypothermia, have been noted.

**Etiology.**—The syndrome is brought about by pathologic alterations in the anterior lobe of the hypophysis. The course of the disease is dependent on the type and severity of destruction of the pituitary structure. The condition not infrequently has its onset after childbirth, and in these cases the underlying cause has been ascribed to septic emboli in the pituitary gland. H. H. Riecker and A. C. Curtis, from a review of the necropsy findings in 24 cases of Sim-

monds' disease, report that the destruction of the pituitary gland was brought about by puerperal sepsis in 9 cases, syphilis in 5 cases, cysts in 4 cases, tuberculosis in 2 cases, and by an unknown agent in 2 cases.

The disease affects both the male and female. However, the incidence in the female is considerably higher than in the male. R. M. Calder (cited by C. W. Dunn: *J. Nerv. and Ment. Dis.* 83:166 (Feb.) 1936), reports a series of cases in which there were 47 females and 18 males, with undetermined sex in 5 cases.

Calder concludes from his study of 70 cases in the literature that syphilis is not definitely established as an etiological factor. Although in many of the reported cases definite pathological changes have been found in the pituitary glands, W. Engelbach<sup>2</sup> maintained that many pituitary cachexias may be caused by transient functional disorders of the anterior pituitary lobe. This view is also held by many other clinicians.

**Prognosis.**—In the cases in which recovery has been reported, it is probable that the disorder in the anterior pituitary lobe was of a functional nature. Cases in which there is marked destruction of the glandular elements almost invariably terminate fatally. A fatal case of Simmonds' syndrome, which had its onset after a long series of frequencies, was reported by Bratton and Feld. Autopsy showed lymphadenoid infiltration of the pituitary gland, with destruction of both the anterior and posterior lobes, and atrophy of the other endocrine glands.

A fatal case of Simmonds' disease was recently reported by E. Rose and G. Weinstein (*Endocrinology* 20:149 (Mar.) 1936). From the pathological appearance alone it could not be determined definitely whether the pituitary, thyroid or adrenal alterations initiated the patient's disease. Death occurred before cachexia had become marked. At

\* See also section on PEDIATRICS: ENDOCRINE DISTURBANCES.

necropsy, marked atrophy, fibrosis and destruction of normal architecture were noted in the anterior pituitary, adrenal cortices, and thyroid.

Recently, L. F. Hawkinson (J. A. M. A. 105:20 (July 6) 1935) and C. W. Dunn (J. Nerv. and Ment. Dis. 83:166 (Feb.) 1936) reported cases of Simmonds' disease in the female with recovery.

In the case observed by Hawkinson, the patient was a school girl, aged 17 years, whose chief complaints were loss of weight, weakness, amenorrhea, somnolence, mental lethargy, falling of the hair, premature aging and dryness of the skin. The patient was given intramuscular injections of anterior pituitary-like gonadotropic principle of pregnancy urine (follutein, Squibb) every other day in doses of 50 rat units. Desiccated thyroid was given by mouth in doses of  $\frac{1}{2}$  grain (0.03 Gm.) 3 times a day. This treatment was continued for 10 days. The patient continued to become progressively worse. The desiccated thyroid was discontinued and the **gonadotropic principle of pregnancy urine** was increased to 150 rat units every other day. In a week she had begun to gain weight and was much brighter mentally, the somnolence was much improved, and she felt better in every way. Treatment was continued for several months during which period there was progressive improvement. The patient received approximately 5000 rat units of gonadotropic principle of pregnancy urine during  $4\frac{1}{2}$  months.

In Dunn's case, the patient was a girl, aged 13 years, who had been suffering from Simmonds' disease for a period of 9 months, and who was presenting progressive and acute symptoms of this condition. At the age of 12 years the child had begun to lose weight, was extremely nervous, and had crying spells. Loss of weight, weakness, and dizziness were pronounced. The menses, which had commenced at the age of 11 years, ceased after the onset of the disease. She complained of polydipsia and polyuria. Her mental state progressed to more marked irritability with periods of depression. Other symptoms were falling out of the hair, dryness of the skin, and lack of perspiration.

A *diagnosis* of Simmonds' disease was made from the following signs and symptoms: acute onset of an illness in a previously healthy mature female, rapid loss of weight (58

pounds), sudden cessation of menses after normal menstruation for over a year, atrophy of the primary and secondary sexual organs, hypotension, vertigo, chilliness, cyanosis of the feet and legs, mental and physical asthenia; the dermal changes, *i. e.*, generalized loss of hair, thickening and dryness of the skin, pigmentation, lack of perspiration; the mental

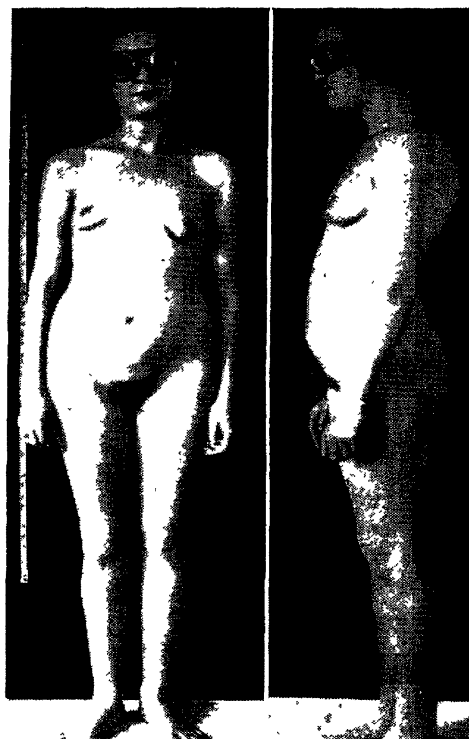


Fig. 3.—Left: Patient in October, 1934, twenty-two weeks after therapy was started; anterior view. Right: The same, lateral view. (C. W. Dunn: J. Nerv. and Ment. Dis.)

symptoms; the progressiveness of the disease at a rapid and uncontrollable rate; headache; anorexia; and gastric pains.

In the *treatment*, the patient received a daily injection of 2 c.c. ( $\frac{1}{2}$  dram) of **anterior pituitary liquid**, except Sunday, and the weekly injection of 10,000 rat units of **female sex hormone (progynon B)**. This therapy was maintained for 3 months, when consistent weight gain, continuous rise of blood-pressure, the onset of menstruation and generalized improvement occurred. The mental state also improved.

After a period of 3 months, when improvement was marked, bi-weekly injections of 2 c.c. ( $\frac{1}{2}$  dram) of anterior pituitary liquid and a weekly injection of the female sex hormone (10,000 rat units) were started. The latter

## SIMMONDS' DISEASE PAGE 13 YRS

THERAPY: ANTERIOR LOBE PITUITARY  
FEMALE SEX HORMONE

WEIGHT LOSS 58 LBS.

AMENORRHOEA 1 YR

GENITAL-  
BREAST ATROPHY

## SYSTOLIC PRESSURE—WEIGHT—CURVE

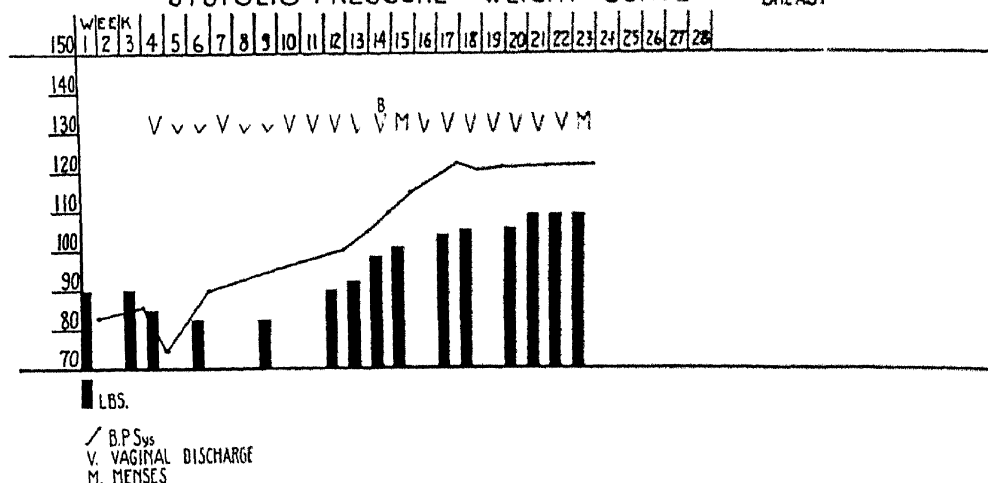


CHART I.—Systolic Pressure and Weight Curve. Note relation of blood pressure rise to weight curve. (C. W. Dunn: J. Nerv. and Ment. Dis.)

will be reduced to 2000 rat units after the third menses.

The administration of the follicular hormone is rational in the dose employed, since it is necessary to use large dosage to combat the rapid and progressive atrophy of the primary and secondary genital organs which is part of the pathological picture of Simmonds' disease.

### THYROTROPIC HORMONE.

—*Physiological Action.*—The administration of pituitary extracts containing the thyrotropic principle has been shown to bring about an increase in *basal metabolism*, according to W. O. Thompson, S. G. Taylor, III, P. K. Thompson, S. B. Nadler and L. F. N. Dickie (Endocrinology 20: 55 (Jan.) 1936). This increase in rate was noted in 32 of 79 observations on 59 patients of various types. The increase occurred in every group of patients in whom there was any thyroid tissue capable of functioning. No increase was noted in 4 patients with marked myxedema; but in patients with mild or moderate thyroid deficiency, the rate could be raised to normal.

The increase in metabolism was always temporary in spite of prolonged treatment. Second series of treatment

usually, but not always, failed to produce an increase in the basal metabolic rate. Thyroxin and desiccated thyroid produced pronounced calorogenic effects after patients had become refractory to the pituitary extracts.

**UTERINE BLEEDING, FUNCTIONAL.**—*Treatment.* In functional uterine hemorrhage the basis for the bleeding seemingly lies in the failure of ovulation to occur and as a result there is a failure in the development of the corpus luteum. In this type of endocrine disturbance it appears logical to assume that corpus luteum therapy (**progestin, proluton, progesterone**) would be extremely beneficial.

In a recent article, K. M. Wilson and C. A. Elden (Am. J. Obst. and Gynec. 32: 94 (Aug.) 1936) presented examples of uterine bleeding associated with endometrial hyperplasia which illustrate certain points in connection with progesterone therapy in this type of bleeding. The progesterone used was the purified hormone prepared from sows' ovaries by Elden according to the method of

Allen and Meyer, the hormone being then dissolved in sesame oil. One rabbit unit corresponded to 1 mg. of the purified crystalline hormone.

Satisfactory results were obtained in 5 cases, but the mechanism by which these results were brought about was not so clear. This group of patients presented varying degrees of uterine hemorrhage and were treated on the assumption that their own production of progesterone was deficient. The dosage of progesterone employed was determined on empirical lines, since at present it is impossible to determine the degree of deficiency of progesterone in an individual.

In one case, the patient aged 32, had recurrent *menorrhagia* following a dilatation and curettage for the same condition. Two doses of  $\frac{2}{25}$  rabbit units given on 2 successive days before the onset of periods resulted in periods of normal duration and amount.

**VIRILISM AND PSEUDO-HERMAPHRODITISM.**—*Male Hormone Content.*—A study of the

“male” sex hormone (comb-growth and prostate-stimulating hormone) in the urine of 11 women with the syndrome of virilism and of 3 pseudohermaphrodites was made by S. L. Simpson, P. de Fremery and A. Macbeth (*Endocrinology* 20:363 (May) 1936). The assay of male sex hormone in the urine was made by noting the effect of the urinary extract on the growth of combs of capons and the weight of the prostates of castrated rats.

An excess of the male sex hormone was found in the urine of 4 of 7 women with adrenogenital syndrome, 3 women with Cushing's syndrome, and 2 of the 3 pseudohermaphrodites. An excess was not found in the urine of 3 patients with adrenogenital syndrome, a woman aged over 50 years with Achard-Thiers syndrome, or a pseudohermaphrodite aged 4 years. An excessive amount was found in the urine of a patient with adrenal hyperplasia (adrenogenital syndrome), a woman with Cushing's disease caused by adrenal carcinoma, and 1 pseudohermaphrodite, caused by adrenal hyperplasia.

## GASTROENTEROLOGY

Edited by HARRY L. BOCKUS, B.S., M.D.

### DISEASES OF THE ESOPHAGUS

By CHEVALIER JACKSON, M.D., Sc.D., LL.D., and  
CHEVALIER L. JACKSON, A.B., M.D., M.Sc.

#### FIBROSIS OF ESOPHAGUS.—

The outstanding advance in the knowledge and conception of esophageal disease is due to the work of Harris P. Mosher (“The Histology and Pathology of the Esophagus with Clinical Applications,” Vol. III, 1936). He has shown that the esophagus is often infected in acute and chronic systemic disease. Infection in the esophagus, as elsewhere

in the body, often results in fibrosis in or about the esophagus. This fibrosis, if extensive enough or rightly placed, results in obstructive narrowing. The lower end of the esophagus is especially liable to infection and fibrosis on account of its nearness to the stomach, gall-bladder and liver—organs often diseased.

Prominent among the diseases in which infection of the esophagus has

been found are arteriosclerosis, nephritis and pneumonia. Superficial ulcerations of the esophageal mucous membrane are constantly in the making. Many are due to the superficial glands breaking through the surface of the epithelium. In other cases the lymphoid follicles enlarge and do the same thing. These ulcerations lie in wait for infection to become pathological ulcers. The superficial vessels of the epithelium when thrombosed may become large enough to extend to the surface and cause a break. These ulcerations are important, because it takes but little to glue the vertical rugæ of the esophagus together, especially at the lower end, to start obstruction. Histological examination shows fibrosis of this portion of the esophagus and a disorganization of the

musculature. In advanced cases a backward bend of the lower end of the esophagus and a vertical twist play an important part in keeping up the obstruction. In some cases these two factors are as important as the fibrosis.

**Dilatation** will give a clinical cure in the majority of cases of fibrosis of the terminal portion of the esophagus. In the old and advanced cases, however, where there is a double bend of the lower end of the esophagus and when the esophageal wall is thin, it is very dangerous to manoeuvre the dilating bag round "dead man's curve" even with the guidance of a swallowed string. These advanced cases are best dealt with by an **anastomosis of the lower end of the esophagus with the fundus of the stomach.**

## DISEASE OF THE GALL-BLADDER

By WILLIAM FITCH CHENEY, M.D.

Recently attention has been called to various investigations indicating that all gall-bladder disease has a common origin in infection, and begins as acute or chronic cholecystitis. The one exception to this is gall-stones, which might originate from faulty cholesterol metabolism, with inflammation following rather than preceding their formation. The frequency of gall-bladder disease is emphasized as well as the conclusion that infection is most often carried to the organ by the blood. The microorganisms found responsible are the streptococcus group or else the colon bacillus and typhoid group. These enter the blood stream from foci in the mouth, nose and throat, or in the large bowel. In diagnosis, cholecystography and duodenal drainage remain the most trustworthy aids; but the carefully taken history is considered equally as important as laboratory methods of investigation.

The trend is toward conservative treatment, leaving surgical removal of the gall-bladder for those cases that fail to respond to dietetic and medicinal therapy, after removal of all foci of infection.

Great interest has continued to be manifested in the subject of gall-bladder disease, as shown by the numerous papers contributed to medical literature. But most of these simply confirm previous knowledge without adding any outstanding new information. One of the most interesting recent discussions of gall-stones is that by A. J. Delario (*Am. J. Digest. Dis. and Nutrition* 2: 511 (Nov.) 1935). This calls attention anew to the fact that while cholesterol is the chief constituent of human *gall-stones*, it is not found at all in concretions in animal gall-bladders or very rarely so. Removed from the blood along the entire gastrointestinal tract but mainly by the



large bowel, its importance is in the gall-bladder, the mucous membrane of which excretes it as one ingredient of the bile. While it is insoluble in water, cholesterol is kept in solution in bile by the bile salts, provided they are present in the proportion of 13 to 1. Prevention of precipitation of cholesterol as nucleus for a concretion or as its sole constituent therefore depends upon two factors: first, that this ingredient of the bile be kept in solution and, second, that stasis in the biliary tract be prevented. The administration of bile salts by mouth accomplishes both purposes, for it stimulates the liver cells to form an increased amount of bile and of bile salts and it keeps the upper biliary tract free from stasis by this greater flow of secretion. Fatty foods likewise stimulate the liver to form more bile and the gall-bladder to empty more promptly, thus aiding in preventing stasis. The other substances found at times in gall-stones, bilirubin and calcium salts, are likewise insoluble in water, but seldom form concretions by themselves unless faulty cholesterol metabolism precedes.

**Etiology.**—One of the still controversial topics concerning *gall-stone* production is whether they form as the result of infection and a preceding cholecystitis, or whether faulty metabolism comes first as a cause of these concretions and these by their presence favor infection and thus induce cholecystitis. B. Halpert and K. B. Lawrence (Surg. Gynec. and Obst., 62:43 (Jan.) 1936) review the histories of 60 patients regarding the relation of clinical manifestations of cholecystitis and cholelithiasis to changes found in the gall-bladder and its contents after operation. If only one of the stone-forming constituents, such as cholesterol, was found in the concretions removed, even though cholecystitis was also observed in all, it was assumed that the cholecystitis followed rather than

preceded stone formation. But in a second group, where the gall-bladder contained mixed concretions, consisting of two or more constituents, the history was of long-standing clinical manifestations with recurring exacerbations; in these it was thought there was a causal relation between chronic cholecystitis and the ultimate production of stones.

**Diagnosis.**—J. R. Twiss and E. C. Hansen (Am. J. Digest. Dis. and Nutrition 3:391 (Aug.) 1936) call attention again to the difficulties and uncertainties of securing *duodenal contents* by means of a tube passed through the mouth and stomach, such as will give reliable cultures, uncontaminated. They show particularly, however, by the investigation of 355 patients not coming to operation, the influence of gastric secretion on the sterility of duodenal contents obtained by intubation. Those who had a hyperchlorhydria showed sterile cultures twice as often as those who had achlorhydria or deficient secretion. Also, in 120 patients who had cultures made directly from the biliary tract at the time of operation, the incidence of infection in those with achlorhydria was about twice that of the group with normal acidity. In patients who showed an infection of the biliary tract, the organisms found preoperatively in pure culture were as usual those of the colon bacillus, typhoid bacillus or streptococcus groups. They conclude that there is a definite relation between gastric acidity and biliary infection.

**Treatment.**—The question as to when *cholecystectomy* becomes advisable still continues to evoke discussion. Further confirmation of the rule that this operation gives better results when cholelithiasis complicates than when cholecystitis alone exists, is supplied by W. D. Wilson, E. P. Lehman and W. H. Goodwin (J. A. M. A. 106:2209 (June 27) 1936). Reporting the results

of gall-bladder surgery in 610 cases, they state that when stones were present satisfactory results were obtained in 79 per cent. of their operations; but when the gall-bladder was stoneless, in only 64 per cent. As regards the diagnostic value of *cholecystograms*, they quote C. B. Rose (Radiology 22:197 (Feb.) 1934), who studied 6268 cases reported by 20 different observers, with the result that gall-bladders found abnormal by cholecystograms showed pathological change after removal in 93.3 per cent.

There is still a difference of opinion about the propriety of early **operation** in *acute cholecystitis*. Twiss and Hansen (*loc. cit.*) consider that the good results from this have not been proved when measured by mortality rates. Other authorities, however, approve and advise it. W. L. Wolfson and R. E. Rothenberg (J. A. M. A. 106:1978 (June 6) 1936) report results of operation on 31 patients with acute noncalculous cholecystitis. Perforation occurred in 6 of the 31 cases. The mortality was 9.6 per cent. in the entire group. This constitutes the most recent report on a total number of 379 cases of acute cholecystitis operated upon by these observers since 1925. About half of these showed no previous attack or any symptom referable to gall-bladder disease. The clinical course was that of a severe, fulminating infection, in most instances, with high temperature, chills, high leukocyte count, pain, tenderness and rigidity in the right upper quadrant, with jaundice in 8 cases, from coincident cholangitis and hepatitis.

J. H. Musser (J. Michigan M. Soc. 35:10 (Jan.) 1936) reviews the *medical management* of gall-bladder disease. He doubts whether it is known that foci

of infection are responsible for cholecystitis, but believes all such **foci** should be **removed** nevertheless; as an aid to improving general health. All reported biliary antiseptics he believes are worthless in overcoming gall bladder infection. **Exercises** to prevent biliary stasis can be carried out as well at home as at European or American Spas and with much less expense; while simple saline cathartics such as **sodium sulphate** or **phosphate** or **magnesium sulphate** do as much good when taken at home as when administered at foreign "cures," from natural springs. He believes gall-bladder drainage by **duodenal tube** is of value mainly because of its psychological effect on the patient. **Diet** must be individualized, depending upon the patient's weight and the possible presence of gastric complications. In general, it should be bland and nonirritating, avoiding fried foods, high seasoning, coffee, chocolate, fresh pastries and bread, and the heavy fibrous and seedy vegetables. Coarse vegetables should be put through a colander and all foods thoroughly masticated. If a low cholesterol diet is indicated, avoid egg-yolk, butter, cream, liver, sweetbreads, duck, meat-fat and salmon. Adjust the number of calories to the patient's bodily nutrition. Fatty foods high in cholesterol should be advised if the gall bladder is functioning poorly, but not if they cause distress. Among drugs, Musser advises **saline cathartics**; a course of **calomel** once in 2 weeks; **alkalies** an hour or two after meals if the patient has hyperacidity; antispasmodics such as **belladonna** for pain, and sedatives such as **bromides** and **barbituric acid preparations** for gastrointestinal symptoms apparently due to nervousness.

## DISEASES OF THE PANCREAS

By THOMAS A. JOHNSON, M.D.

The present unsatisfactory status of the various *pancreatic enzymatic function tests* is reflected in the 1934 report of the Enzyme Committee of the American Gastro-Enterological Association. Twenty-two different tests were used by only 27 members of the Association. Widely divergent views obtained concerning the actual value of any of the proposed tests.

Much of the recent work on the clinical estimation of pancreatic function centers around four approaches, *i. e.*: (a) estimation of the enzymatic activity of the duodenal fluid; (b) estimation of the blood enzymes; (c) estimation of enzymes in the urine; (d) examination of the stool for evidence of faulty fat digestion.

A study of the various methods for estimating the enzymatic activity of duodenal fluid collected in accordance with the Lyon technic reveals a number of sources of possible error among which are the uncertainty concerning the amount of pancreatic juice in the sample, the dilution factor, and the possible contamination with other enzymes, especially salivary amylase. The wide variations encountered in normal subjects detracts from the value of any single determination of the enzymatic activity of the duodenal fluid.

There is by no means a universal agreement that all three of the principal pancreatic enzymes are always excreted in equal concentrations. The work of McClure and his co-workers indicates some degree of specificity of response of trypsin, amylase and steapsin, depending on whether or not the stimulus in the duodenum is predominately protein, carbohydrate or fat. On the other hand, Baxter concludes that all three enzymes are excreted in parallel con-

centrations. The importance of that consideration is apparent when a review of the current literature indicates that the majority of clinical workers in that field are basing their conclusions on observations of only one of the three principal pancreatic enzymes. A thorough study of a large series of clinical cases using routine estimations of the three enzymes would be enlightening.

Much of the work on the duodenal fluid estimation of pancreatic enzymes centers about the *determination of amylase*. McCaughan reviews the previous work on amylase, calling attention to the earlier work of Payen and Persoz (1803), who first precipitated a starch splitting enzyme from malt, calling it diastase; Magendie (1846), who showed that blood was capable of splitting starch into sugar; Foster (1867), who first measured diastase quantitatively in animals; Wohlgemuth (1908), who developed a practical quantitative method of amylase determination based on the starch-iodine reaction; Northrup and Hussey, who developed a viscometric method of estimating trypsin which Davison first applied to amylase.

Schmidt, Greengard and Ivy, after comparing the various methods for the quantitative estimation of *diastase in the duodenal fluid*, concluded that their modification of the Willstatter method was the most practical. Most workers agree with A. C. Ivy (J. A. M. A. 105: 506 (Aug. 17) 1935) that the Wohlgemuth method of determining amylase is of qualitative value and cannot be depended upon for accurate quantitative work.

In a review of the present status of gastrointestinal principles, Ivy comments on the recent studies of *secretin* by Chiray, and Voegtlin, Greengard and

Ivy, suggesting the possibilities of the use of that substance in estimating pancreatic function. Further studies on secretin within the next few years will be awaited with interest.

Recent *enzymatic blood studies* with reference to pancreatic function are concerned largely with *amylase* and *lipase*. Worthy of note is an apparent discrepancy in the clinical case reports from various workers using either the viscometric or one of the other methods of estimating blood amylase. L. A. Crandall, Jr. (*Am. J. Digest. Dis. and Nutrition* 2:230 (June) 1935), postulates the presence of at least two types of blood amylase, one active in the initial hydrolysis of the starch molecule (liquefying amylase, which is estimated by the viscometric method), the other producing the reducing sugars that are the end-products of starch digestion (saccharogenic amylase). Crandall further states that in *acute pancreatic disease* or experimental *pancreatic obstruction*, the liquefying amylase of the blood is increased, but there is no change in the saccharogenic amylase; in chronic pancreatic disease with failure of enzyme formation, or after experimental pancreatectomy, the liquefying amylase of the blood may be decreased apparently without change in the saccharogenic amylase. Crandall's thought in that matter would seem to fit in with some experimental work of McCaughan who, using a viscometric method of determining blood amylase in dogs, found the height of the rise directly proportional to the degree of occlusion of the pancreatic ducts or to the extent of the parenchyma involved in the inflammatory process, noting in duct ligation a maximum rise within 72 hours, which was maintained at the most only 8 to 15 days. In *duct obstruction* McCaughan ascribes the rise in blood amylase to overdistention of the ducts, calling at-

tention to the fact that continued distention over a period of time causes atrophy and degeneration of the gland tissue, which accounts for the later decrease in blood amylase. *Inflammatory processes*, however, gave the highest blood diastase values, which McCaughan attributes to swelling of the acini and lining of the ducts. Total *pancreatectomy* caused a temporary fall in blood diastase to approximately 20 per cent. of the preoperative level, but curiously enough the level quickly returned to normal, a phenomenon which McCaughan is at a loss to explain, but he suggests that more study is needed to throw light on the primary source of blood amylase.

Indeed, it has been suggested that under certain conditions blood amylase might arise from the *parotid gland*, in spite of some experimental work to the contrary, a possibility which, if true, would ultimately cast some doubt on the value of any blood diastase test as an index to pancreatic function.

Classen, Johnstone and Orr, confirming the observations of McCaughan on blood amylase, call attention to the variability of the starch substrate, to which they ascribe some of the discrepancies of different workers, starch being a mixture of alpha amylose, beta amylose and dextrins in such varying proportions that it is difficult to reproduce an identical mixture.

The *estimation of blood lipase* has received much attention in the past few years because, among other reasons, the method employed is relatively simple as compared with the complicated procedure adopted in connection with other enzymes. Cherry and Crandall review the literature on blood lipase and present their modification of the Loevenhart method which forms the basis of most of the estimations by other workers. These authors call attention to some

earlier work differentiating serum lipase from serum esterase, suggesting that the term "*lipase*" be reserved for the enzyme (or enzymes) capable of splitting true fats and oils, and that the term *esterase* be used for the enzyme (or enzymes) acting upon simple esters." Lipase requires a true fat or oil as a substrate (olive oil), while esterase is measured by its effect on a simple ester, such as ethyl butyrate or tributyrin. Cherry and Crandall, in the same paper, quote Hanriot (1897), Doyan and Morel (1902), and Arthus (1902) to the effect that true lipase is absent from normal blood, while esterase is usually present. M. W. Comfort (Proc. Staff Meet., Mayo Clin. 10:810 (Dec. 18) 1935) differs with the observations of Crandall and with those reported by Jergeson and Simmonds, in that he found serum lipase present in small amounts in all the normal serums he studied. Comfort reports the normal blood lipase ranging from 0.2 c.c. to 1.5 c.c. of one-twentieth normal sodium hydroxide per 1.0 c.c. of blood serum. Comfort and Osterberg present the details of their technic and the results of a series of pathologic cases, concluding that a reading above 2.0 c.c. of one-twentieth normal sodium hydroxide per 1.0 c.c. of blood serum is definite evidence of disturbed pancreatic function.

Comfort (*Ibid.*) in cases of *acute pancreatitis* observed blood lipase values up to 10.0 c.c. which, however, rapidly dropped to normal within several weeks. The same author observed an increase in serum lipase values in 50 per cent. of their cases of *malignancy of the pancreas*, which, however, were not as high as those found in inflammatory conditions of the pancreas but had a tendency to remain elevated over a longer period. Whether or not the increase in blood lipase values in pancreatic malignancy

is due entirely to duct obstruction or associated secondary inflammation is uncertain. Comfort concluded that the determination of serum lipase has proved of greater value in the diagnosis of *acute or subacute inflammation of the pancreas* than any other procedure he has used. Crandall, in a summary of the current thought on blood serum enzymes, calls attention to the marked increase in blood lipase in experimental *pancreatic duct obstruction*, an observation on which most observers appear to agree.

H. L. Popper, *testing the gall-bladder bile for diastase* by the Wohlgemuth method in 219 cases, concluded that pancreatic juice frequently flows into the bile ducts from the pancreatic ducts, but that its presence is not pathologic unless there is some obstruction to the flow of the bile-pancreatic mixture, in which case the activated mixture is the most frequent cause for the origin of acute affections of the pancreas. Popper observed that normal bile contained diastase equal in amount to that found in normal blood.

A. W. Oelgoetz, P. A. Oelgoetz and J. Wittekind (Am. J. Digest. Dis. and Nutrition 2:422 (Sept.) 1935; 3:159 (May) 1936) report some studies which they believe indicate that certain phases of *allergy* are related to the absorption into the blood stream of incompletely digested food products which are normally carried on to complete digestion by the blood enzymes, but in the absence of the normal level of blood enzymes, give rise to allergic symptoms. They further report clinical improvement in such cases by administration by mouth of adequate amounts of a 50 per cent. **glycerin extract of whole pancreas**.

R. W. Keeton (M. Clin. North America 18:1297 (Mar.) 1935) reported the clinical findings in 30 cases of pancreatic disease. He believes that

any of the present *enzymatic tests* on the duodenal fluid, blood, or urine are unreliable in many cases because the normal enzyme capacity of the pancreas is so great that a drastic reduction in secretion might occur before any disturbance can be detected by the ordinary methods now in use. Keeton feels that the history of the patient usually is the most suggestive finding in the average pancreatic case. Of the objective findings, Keeton notes that the presence of an excessive amount of neutral fat in the stool in the presence of adequate amounts of bile is suggestive of a lack or decrease in the amount of pancreatic lipase, and therefore, indicative of impaired pancreatic function. The validity of the above observation, of course, is predicated on the exhibition of normal bowel motility.

H. Blotner (J. A. M. A. 106:1970 (June 6) 1936) presents some experimental evidence to support the observations of others that *alcoholic polyn neuritis* or *deficiency disease* may be caused in part at least by faulty digestion and assimilation of food resulting from the destruction of digestive enzymes by large quantities of alcohol taken over a considerable period of time. Blotner's first studies, done *in vitro*, were confirmed by similar observations in chronic alcoholics in whom he found an achlorhydria following a heavy alcoholic drinking bout. However, the addition of hydrochloric acid to the achlorhydric specimens failed to influence the results of the test. Blotner concluded that alcohol rather than achlorhydria was the important factor in the destruction of the digestive enzymes.

## JAUNDICE

By HENRY J. TUMEN, M.D.

**Classification.**—Although there was much to recommend Rich's division of all cases of jaundice into two main types—retention and regurgitation icterus—a continued use of the earlier classification of McNee would simplify the problem for the clinician. When patients are thought of as having hemolytic or obstructive or toxic-infectious (hepatocellular) jaundice, a clear conception may be found of the diagnostic and therapeutic problems presented. This is also the conclusion of R. Ottenberg (J. A. M. A. 104:1681 (May 11) 1935) who calls attention to the fact that the two types of icterus which are most difficult to differentiate from each other, the obstructive and the hepatocellular, fall into the same large group in Rich's plan, that of regurgitation jaundice. It is felt, therefore, that for reasons of convenience and clarity the simpler

classification of McNee should be retained.

**Bilirubinemia.** Various features of the essential physiological change in jaundice, the accumulation in the blood stream of an excessive amount of bilirubin, are still the subject of active investigation. A. Jores (Ztschr. f. klin. Med. 129:62, 1935) found a definite fluctuation in the serum bilirubin level throughout the day, and ascribed the variations to rhythmic changes in liver activity. K. Fellingner and R. Pfleger (Wien. Arch. f. Inn. Med. 26:321, 1935) noted that the blood bilirubin increased during periods of fasting and decreased after meals. These alterations were thought to be responses to falls and rises of bile secretion.

The inadequacies of the van den Bergh test and the difficulties in selecting an entirely satisfactory technic and

choosing suitable standards have been emphasized by Magath, who recalled that it furnished merely an "estimation" of the serum bilirubin level. During the past few years a number of workers have devoted themselves to attempted solutions of the technical problems that this test presents. The most recent work of importance along this line has been done by E. G. Godfried (Biochem. J. 29:1337 (June) 1935) and by A. S. Giordano and D. Eager (Am. J. Clin. Path. 6:286 (May) 1936). In most instances it is advised that a technic based on the modification of Thannhauser and Anderson be used, since this decreases the bilirubin loss at the time that the serum proteins are precipitated. Despite its imperfections, the van den Bergh test is preferred to the icterus index by most investigators.

Kerppola and, more recently, B. Varela-Fuentes, M. C. Rubino and C. Viana (Compt. rend. Soc. de biol. 118:1520, 1935) have described methods for measuring separately the amounts of direct and indirect reacting bilirubin in the blood. Such methods may have diagnostic value, since indirect reacting pigment is said to be increased in many cases of jaundice due to hepatic insufficiency as well as those of hemolytic origin. (B. Varela-Fuentes and C. Viana: *Ibid.* 118:927, 1935; H. M. Rozendaal, M. W. Comfort, A. M. Snell: J. A. M. A. 104:374 (Feb. 2) 1935). B. Varela-Fuentes and C. Viana (Compt. rend. Soc. de biol. 118:1518, 1935) also report the discovery of a curious type of indirect reacting bilirubin, extractible by ether, that they found chiefly in patients with malignant growths of the biliary passages.

**Liver Function Tests in Diagnosis of Jaundice.**—Careful consideration of the patient's history and of the clinical findings will frequently suffice to determine the cause and mechanism of

jaundice. Occasionally, however, it is impossible to do this, at least early in the course of the illness, without the assistance of some test of liver function. Many tests have been investigated during the past few years. Although they are by no means infallible, the information they give is often of value. Those more frequently used will be discussed briefly.

**Galactose Tolerance Test.**—In the earlier discussions of this test, its technic and physiological background, it was stated that its diagnostic value depended upon the frequency with which it is positive in cases of icterus due to acute liver cell damage and the rarity with which such a result is seen in obstructive jaundice. Banks, Sprague and Snell found, however, that while galactose excretion was high in most cases of acute or subacute intrahepatic icterus, similar readings were obtained in 46 per cent. of jaundice due to malignant obstruction and in 32 per cent. of cases in which the cause of the obstruction was a benign lesion. These positive results occurred in patients in whom extensive hepatic injury was subsequently found. These authors felt that while high excretion of galactose (6 or more grams) indicated either hepatocellular jaundice or severe liver injury in association with obstruction, the diagnostic value of the test was limited. Bensley similarly decided that only marked decrease in galactose tolerance favored a diagnosis of infectious or toxic jaundice and that slightly abnormal excretion of the sugar might be found in any type of icterus.

On the other hand, other recent writers stress the diagnostic assistance given by the use of galactose. Owens, Rosenberg, and Schiff found the test negative in all patients with mechanical jaundice examined and it was negative in 91 per cent. of F. W. White's (Tr. A. Am.

Physicians 50:111, 1935) cases of this type. All of these investigators and also M. Brulé and J. Cottet (Presse Méd. 43:1705 (Nov. 2) 1935) report positive responses in a very high number of patients with toxic or infectious jaundice, including so-called catarrhal jaundice. Such reports justify continued confidence in the use of the galactose test in the diagnosis of jaundice due to liver cell injury, although it must be realized that the test is occasionally negative even in the most severe hepatic disturbance and also sometimes positive in obstructive jaundice if extensive damage to the hepatic parenchyma has supervened.

In an attempt to eliminate errors that might interfere with the accuracy of the ordinarily performed galactose test, Jankelson and Lerner advise studying the blood sugar changes after the intravenous administration of galactose. It is questionable whether the value of the test is enhanced sufficiently by this method to warrant the added trouble.

*Blood Phosphatase Determination.*—The phosphatases are enzymes that are normally present in most of the body tissues and also the bile, feces and blood. They play an important part in bone metabolism. It is probable that the bony tissue is the chief if not the only site of phosphatase origin, although they may also be formed in the intestinal mucosa, liver, kidneys and muscle. It seems quite definitely established that to a large extent they are excreted through the liver into the bile.

In 1930, W. M. Roberts noted a rise in blood phosphatase in 3 cases of icterus. In a later study he found that in patients with obstructive jaundice the rise was much greater than those with icterus due to toxic or infectious changes in the liver and concluded that phosphatase determination might be of value in the differential diagnosis of jaundice.

Since then a number of investigations of the blood phosphatases in both clinical and experimental icterus have been published. (A. R. Armstrong and E. J. King: Canad. M. A. J. 32:379 (Apr.) 1935; R. G. Anderson: St. Barth. Hosp. Rep. 68:221, 1935; F. K. Herbert: Brit. J. Exper. Path. 16:365 (Aug.) 1935; M. M. Rothman, D. R. Meranze and T. Meranze: Am. J. M. Sc. 192: 526 (Oct.) 1936.)

It is unfortunate that there is as yet no universally accepted technic for blood phosphatase determination. Four different methods suggested by Roberts, Jenner and Kay, Bodansky and Armstrong and King are in use. While these all measure the amount of inorganic phosphate formed when the blood enzymes act on a phosphoric acid ester substrate, they differ so in technical details that it is extremely difficult to compare the results of work done with different methods and the conclusions so drawn.

Practically all reports of studies in clinical jaundice indicate that there is a definite rise in blood phosphatase when this is due to obstruction. This is presumably due to accumulation in the blood of enzymes mechanically barred from excretion in the bile. There is no general agreement as to whether or not phosphatase rise parallels that of serum bilirubin following obstruction. Since the two substances differ in sites and rate of formation and in excretability by the kidneys, a definite parallel in accumulation is hardly to be expected.

Marked differences of opinion exist as to the blood phosphatase levels in toxic and infectious jaundice and, therefore, as to their value in differentiating these from icterus due to biliary block. Bodansky and Jaffe, also Greene, Shattuck and Kaplowitz, concluded that phosphatase determination had little to offer from a diagnostic standpoint, since



they obtained high readings in all types of nonhemolytic jaundice. Both Anderson (*loc. cit.*) and Herbert (*loc. cit.*) found higher phosphatase levels in obstructive than in nonobstructive icterus, but noted so much overlapping of the readings in the two groups that they felt the chief diagnostic importance of the test was due to the fact that low results were not seen in mechanical jaundice. A better opinion as to the diagnostic utility of this test was held not only by Roberts, but also by Armstrong and King (*loc. cit.*) and, more recently, by Rothman, Meranze and Meranze (*loc. cit.*). The latter authors, using a modification of Roberts' method, found that in most cases of obstructive icterus the phosphatase readings were greater than 10 units, while in the non-obstructive cases the readings were usually 10 units or less. They state that diagnostic difficulties might be encountered occasionally if only single determinations of the phosphatase level were made. They advised that these could be avoided by repeated examinations to find the trend of enzyme curve or by a comparison of the amount of phosphatase with that of serum bilirubin, since marked bilirubinemia in association with no or only slight phosphatase increase was found to be characteristic of hepatocellular jaundice. Review of the literature and familiarity with many of the cases studied by Rothman and his coworkers would suggest that the conclusions drawn by them are correct and that if certain precautions are observed the blood phosphatase determination is of definite use in the differentiation of the types of jaundice. It is to be hoped that standardization of technic will permit more satisfactory comparison of subsequent reports.

**Hippuric Acid Test.**—This test is based upon the synthesis of hippuric acid in the liver following the admini-

stration of sodium benzoate. The effect of hepatic injury upon hippuric acid formation was first noted by Bryan. Experimental work has indicated that in human beings the liver is probably the chief site of manufacture of this substance, as it is in the rabbit, and Quick's studies would seem to show that the rate of its production is dependent on the amount of glycine available. Others, however, have noted a decrease in hippuric acid excretion by rabbits with damaged livers, even if excessive glycine was fed with the sodium benzoate. Clinical application of this test has been the result of Quick's investigations and the technic is described in his recent article (*Arch. Int. Med.* 57:544 (Mar.) 1936). Briefly, it consists of determining the amount of acid excreted within 4 hours following the administration of 5.9 Gm. ( $1\frac{1}{2}$  drams) of sodium benzoate. This is normally about 3 Gm.—45 grains (range from 2.55 to 3.3 Gm.—39 to 50 grains).

The relation of kidney function to hippuric acid excretion has been considered by Snapper and Grünbaum as well as by Quick (*loc. cit.*). The former found renal disease to have no influence on elimination of this substance unless the urea nitrogen of the blood was elevated and the latter claimed that the kidneys can excrete hippuric acid about 50 per cent. faster than the liver can form it, so that only severe renal damage can affect the result of the test.

Quick reported a decrease in hippuric acid excretion by patients with parenchymal liver disease, so that positive results were obtained in the presence of catarrhal jaundice, toxic hepatitis, luetic cirrhosis and metastatic carcinoma. Normal excretion occurred in obstructive icterus unless this had been present for long periods. P. F. Vaccaro (*Surg., Gynec. and Obst.* 61:36 (July) 1935) noted that when the test was positive

in mechanical jaundice, gross structural changes were found in the liver at operation. A. M. Snell and J. E. Plunkett (Am. J. Digest. Dis. and Nutrition 2:716 (Feb.) 1936) concluded that hippuric acid synthesis was a reasonably accurate index of parenchymatous hepatic damage and that it was of particular value in measuring the liver's functional state in the "surgical" types of jaundice.

The reports of D. Adlersberg and H. Minibeck (Ztschr. f. d. ges. Exper. Med. 98:185, 1936; Ztschr. f. klin. Med. 129:392, 1936), which were based on an extensive study of patients with and without hepatic disease, did not assign such great diagnostic value to this test. While the results were positive in patients with hepatocellular disease, similar readings were the rule in the presence of obstructive icterus, cardiac decompensation, anemia and wasting diseases, and these were ascribed to defects of absorption or excretion. They concluded that a normal response to the test indicated that liver function was relatively good and that in a patient with known hepatic injury the method would serve to follow the progress of the disease, but that when the diagnosis was in doubt, low excretion of hippuric acid would be of little diagnostic assistance. It seems true at the present time that a normal hippuric acid synthesis is of value in obstructive jaundice in indicating preservation of good liver function. Further studies upon patients with non-hepatic disease are needed to determine the full diagnostic worth of low excretions of the acid.

**Blood Cholesterol Levels.**—In hepatic degenerative disease there is frequently found a lowering of the cholesterol esters and a decrease in the ratio of the cholesterol esters to total cholesterol. Epstein's work emphasized the diagnostic importance of this finding and

Laroche also considered it to be of great utility. Ottenberg (*loc. cit.*) felt that much reliance could be placed upon the cholesterol partition in the differentiation of obstructive and hepatocellular jaundices. It must be noted, however, that determination of cholesterol and its esters is a complicated chemical procedure, and it is questionable whether this gives more diagnostic information in jaundice than a simpler test such as galactose tolerance.

**Bilirubin Tolerance Test.**—This test is based upon earlier studies of von Bergmann and Hilbott. It was first used in this country by Harrop and Barron. It consists of determining the speed with which intravenously injected bilirubin disappears from the blood stream. Details of a simplified technic will be found in a recent article by L. J. Soffer and M. Paulson (Am. J. M. Sc. 192:535 (Oct.) 1936). Since bilirubin is the substance which the liver normally excretes, this test rests upon a sound physiological basis. It has been claimed to be definitely more sensitive than other liver function tests (L. J. Soffer: *Medicine* 14:185 (May) 1935; K. Pröchner-Mortensen: *Acta Med. Scandinav.* 85:1, 1935). This test cannot be used, however, in patients jaundiced to the degree of having bilirubinemia, since it is impossible to be certain in such cases that the extra bilirubin has actually been excreted by the liver and not by the kidneys. On the other hand, the method has been of real use in discovering the existence of residual liver damage after jaundice has subsided.

**HEMOLYTIC JAUNDICE.**—A systematic review of *congenital* hemolytic jaundice has been presented recently by L. M. Hurxthal (*Clin. North America* 15:1475 (Dec.) 1935). In an earlier paper the Cheneys stressed as almost diagnostic of this condition the occurrence of pronounced microcytosis

in the presence of jaundice. The importance of the abnormalities of the red blood cells is also emphasized by other investigators. W. J. W. Paxton (Arch. Dis. Childhood 10:421 (Dec.) 1935) noted the globular shape of the cells and the increase in hemoglobin per corpuscle. Haden studied the changes that occur in normal erythrocytes when placed in hypotonic saline and noted that they became more globular with little change in diameter. He found that the red cells in congenital hemolytic jaundice show microspherocytosis and concluded that in this disease the erythrocytes have, to begin with, one of the shapes through which normal cells pass in saline dilutions and so may be regarded as that much nearer the hemolysis point. Haden regarded this microspherocytosis as the one basic variation from normal in hemolytic jaundice—all other features of the disease were considered to be secondary to it. Such an opinion receives confirmation from the report of Hawksley and Bailey, that in a newborn child, lowering of the mean diameter of the red cells and increase in cell fragility preceded the development of other evidences of the disease. Increased erythrocyte fragility persists after splenectomy. There is, however, some increase in red cell diameter after the operation, although this does not reach normal. These findings suggest that neither red corpuscle changes or splenic overactivity alone is entirely responsible for the clinical features of the disease, but that they may result from action of the spleen on already defective cells. The recurrences after splenectomy are probably due to the taking over by other portions of the reticulo-endothelial system of some of the spleen's activities.

#### **OBSTRUCTIVE JAUNDICE.—**

Snell investigated the hepatic parenchymal lesions that develop in patients with obstructive jaundice. He concluded

that the two chief obstacles to recovery from such jaundice is the development of either acute destructive or degenerative changes in the liver or of marked degrees of biliary cirrhosis and obliterative cholangitis. He felt that only rapid destruction of the hepatic cells would interfere with ordinary metabolic activity. The metabolic liver function tests would be of little value, therefore, and he suggested that more reliance be placed upon an excretory test, such as the serum bilirubin level, to indicate liver insufficiency. A. Cantarow and H. L. Stewart (Am. J. Path. 11:561 (May) 1935), however, in a study of experimental obstructive jaundice, noted no correlation between the morphological changes in the liver and bile ducts and the blood bilirubin concentration.

E. J. Klopp and A. Cantarow (Clin. North America 16:531 (Apr.) 1936) reported a high incidence of hyperbilirubinemia in noncalculous cholecystitis and also cholelithiasis, even when the stones were confined to the gall-bladder. They attributed this to associated hepatitis or intrahepatic cholangitis and felt that these factors likewise contributed to the production of jaundice that occurs with common-duct stone. Their paper emphasizes the difficulty of recognizing the existence of hepatic dysfunction in obstructive icterus. It is to be hoped that such newer tests as the excretion of hippuric acid will be of assistance here.

The presence of marked liver damage in obstructive jaundice is probably of great importance in producing such a complication as *postoperative hemorrhage*. Clute and Swinton reported that bleeding followed operation in 25.8 per cent. of 58 jaundiced cases and that it was a factor in causing death in 5 cases. None of these deaths, however, occurred in a patient with a curable lesion. A. C. Ivy, P. Shapiro and P. Melnick

(Surg. Gynec. and Obst. 60:781 (Apr.) 1935) stated that one-half of all post operative deaths in jaundice are a result of hemorrhage. Despite numerous efforts to find a satisfactory explanation for such bleeding, none is available at present. A. Barlik (Arch. f. klin. Chir. 176:656, 1933; Klin. Wchnschr. 13:102 (Jan. 20) 1934), decided that liver damage permits an overflow into the blood of antiprothrombin and A. J. Quick (J. Biol. Chem. 109:113-114 (May) 1935) was of the opinion that in obstructive jaundice the prothrombin is decreased. (A. J. Quick, M. Stanley-Brown and F. W. Bancroft: Am. J. M. Sc. 190:501 (Oct.) 1935.) Studies directed by I. S. Ravdin, C. Riegel and P. J. Morrison (Ann. Surg. 101:605 (Jan.) 1935) and by Ivy (*loc. cit.*) seemed to indicate that changes in the calcium, fibrinogen, platelets, prothrombin, antiprothrombin, sedimentation rate etc., are not sufficient to account for the occurrence of hemorrhage. Variations in these were seen with equal frequency in icteric patients with and without bleeding tendencies. Carr and Foote have carried out studies which indicate that accumulation in the blood of cysteine or a similar substance may be responsible for the coagulation defect in obstructive jaundice. It was found that brombenzene, which combines with cysteine, reduced the hemorrhagic tendency in experimental animals. The value of glucose therapy in obstructive jaundice might result from suppression of the production of cysteine after sugar administration, as Ravdin and his associates suggested.

After deciding that such measures as the sedimentation rate and clotting indices are inaccurate in warning of a hemorrhagic tendency, Ivy and his co-workers (*loc. cit.*) elaborated a modification of the Duke bleeding time for this purpose. This consists of making

punctures with a stylet 2.5 mm. long in the forearm below a blood-pressure cuff set at 40 mm. of mercury. In normals the bleeding time under such conditions is rarely over 180 and never more than 240 seconds. In some jaundice cases it was found to be definitely prolonged and these patients bled post-operatively. This prolongation was considered to be dependent on the degree of liver damage, rather than on the height of the jaundice.

In the *preparation of the jaundiced patient for operation*, the use of a diet high in carbohydrate and low in protein is universally recommended. This has ample experimental as well as clinical justification. F. C. Mann and J. L. Bollman (J. A. M. A. 104:371 (Feb. 2) 1935) reported the poor tolerance of dogs with complete biliary obstruction to protein feedings and their longer survival when given carbohydrates. The diet is to be supplemented by **glucose** intravenously, particularly during the 3 to 6 days immediately preceding operation. In this period it is wise to give from 100 to 300 grams (3½ to 10 ounces) of glucose and 2500 to 3000 c.c. (2½ to 3 quarts) of **fluid** daily in order to insure ample glycogen deposition in the liver. **Transfusions** should be used in preparing for operation, especially in those patients in whom the presence of long-standing and marked jaundice makes the occurrence of hemorrhage probable. **Calcium** is still used intravenously before operation by many, though actual proof of its value cannot be adduced.

Evidence of *deficiency of vitamins A and D* has often been seen in obstructive jaundice. T. Brugsch (Med. Klin. 31:366 (Mar. 22) 1935) mentions finding visual disturbances as a result of A-avitaminosis in long-standing mechanical icterus. M. D. Altschule (Arch. Path. 20:845 (Dec.) 1935) found microscopic

changes indicative of such deficiency in 6 of 11 children with congenital atresia of the bile ducts, despite the use of diets high in vitamin A. He advised the parenteral administration of the **vitamin** or its use by mouth in conjunction with **bile salts**. Greaves and Schmidt had previously suggested that the bile acids act as carriers for absorption of vitamins A and D across the intestinal wall. With this work in mind, R. W. McNealy, P. Shapiro and P. Melnick (Surg. Gynec. and Obst. 60:785 (Apr.) 1935) gave **viosterol 250D** in doses of 90 drops daily to jaundiced patients. **Bile salts** were also given to those with acholic stools. **Glucose** and **calcium** were administered only sporadically to both the control group and that under investigation. The modified bleeding time mentioned above was used as an index of response. It was reported that these measures resulted in decrease of the bleeding time to normal in from 4 to 7 days in all except very severe and fulminating cases and that the incidence of hemorrhage was definitely lowered thereby in icteric patients.

The **intravenous glucose** should be **continued** for a number of days **following operation**, since bleeding may not occur immediately, but only after the lapse of from 3 to 9 days. If there are *hemorrhages*, frequent **transfusions** are necessary, and two or more daily may be given. **Calcium** may also be given at this time, but chief reliance is to be placed upon the glucose and transfusions.

In discussing the **surgical management** of obstructive jaundice, particularly that due to carcinoma of the head of the pancreas, Lahey favors operation in all cases in which the gall-bladder is dilated, since he has encountered survivals for as long as 4 years after anastomotic procedures. He prefers

**anastomoses of the gall-bladder to the jejunum** rather than to the stomach or duodenum and uses **preliminary decompression** in cases of long-standing jaundice with marked liver damage. A. O. Whipple (Pennsylvania M. J. 39: 473 (Apr.) 1936) has devised an operation for **resection of the malignant portions of the pancreas** that offers some hope of permanent cure of these patients.

**HEPATOCELLULAR JAUNDICE.**—The problem of liver damage by *cinchophen* has been reviewed by Weir and Comfort and by Block and Rosenberg. The former noted that the toxic effects of cinchophen on the liver are indistinguishable from the changes produced by other hepatic poisons. They also remarked that the drug might produce toxic cirrhosis without jaundice. W. L. Palmer and P. S. Woodall (J. A. M. A. 107:760 (Sept. 5) 1936) now conclude that there is no safe method of cinchophen administration and found that even small doses might do **great damage**.

R. J. Sager (Arch. Int. Med. 57: 666 (Apr.) 1936) has investigated the problem of jaundice *in syphilis* and the relation of its occurrence to the use of the *arsenicals*. His article comprises a review of the entire literature on this subject and stresses the increase in icterus in luetics since the introduction of arsenicals. It is this author's thought that the jaundice is the effect of liver injury by these drugs. Sager also discusses the relation of arsenical icterus to so-called catarrhal jaundice and concludes that the toxic action of the arsenic may be more widely seen during epidemics of catarrhal jaundice since this, like other conditions which injure the hepatic cells, may make the livers of those receiving antiluetic treatment more sensitive to the drug.

The condition known as *catarrhal jaundice* still remains an unsolved problem in many respects. Numerous authors now feel that this term does not apply to a single disease entity, but that it includes two separate types of icterus—one obstructive in nature and due to true catarrh of the duodenum and the biliary passages, and the other the result of disturbances of the hepatic cells themselves. This opinion has been expressed by Adler and zu Jeddloh, Hurst and also by Bockus and Tumen. Various liver function tests were used to demonstrate the differences that exist between the two types of icterus. In the REVIEWER's experience, most cases of catarrhal jaundice have been due to hepatocellular damage, but the proportion of the different types probably varies widely with changes in time and place.

The *etiology* of catarrhal jaundice is as yet unknown. It is probable that Brugsch is correct and that no single causative agent exists, at least none that is responsible for both those cases due to catarrhal changes in the ducts and those due to liver cell disease. The mechanism of the former type seems to be that of an ordinary obstructive jaundice. The pathogenesis of the icterus in the cases ascribed to hepatocellular change is not clear. J. Faltitschek (*Ztschr. f. klin. Med.* 128:480, 1935) claims that under these circumstances there is an acute serous hepatitis with marked edema that produces nutritive changes in the liver parenchyma. He stated that he was able to further decrease the hepatic function in catarrhal jaundice by histamine injections, which presumably increased the serous exudate in the liver.

Numerous liver function *tests* have been used in catarrhal jaundice and the positive responses to these, notably the galactose test, emphasize the frequency with which hepatic dysfunction occurs.

Hepatic functional studies in patients who have previously had the condition indicate that the liver insufficiency may occasionally continue for some time after apparent clinical recovery. Thus, W. Ruhbaum and W. Matheja (*Klin. Wchnschr.* 14:1568 (Nov. 2) 1935) obtained positive results to the galactose and levulose tests and particularly to the bilirubin tolerance test in patients in whom there had been complete recession of clinical evidence of the icterus. Soffer and Paulson found delayed bilirubin excretion in 9 of 11 patients who had had catarrhal jaundice from 3 months to 18 years before. Such studies justify the thought that this condition may be the precursor of serious liver disease, such as toxic cirrhosis, as Pratt and Stengel and Myassnikow have already reported.

All studies indicate that the most important measure in the *treatment* of hepatocellular damage is the administration of large amounts of carbohydrate, notably glucose, since many hepatic functions depend on an ample glycogen deposition in the liver. Althausen recommended that in addition to a **diet high in carbohydrate**, these patients be given from 50 to 100 Gm. ( $1\frac{1}{2}$  to  $3\frac{1}{4}$  ounces) of **glucose in fruit juices** 3 times daily. If this cannot be taken by mouth, glucose solution may be given by vein to bring the total daily carbohydrate intake up to 300 to 500 Gm. (10 to  $18\frac{2}{3}$  ounces). The intravenous solution should be given slowly and well diluted. It is now felt rather widely that insulin should not be given with the glucose, since this probably reduces the liver glycogen. The diet should not only be high in carbohydrate, but also low in fat and protein. On the basis of Quick's work it has been recommended that 5 to 10 Gm. ( $1\frac{1}{4}$  to  $2\frac{1}{2}$  drams) of **gelatin** be given daily, since this contains readily avail-

able glycine which the liver may use for detoxifying purposes. Other therapeutic measures include an **ample fluid intake**, **calcium** intravenously and

frequent small **transfusions**. The administration of any drug known to be hepatotoxic should, of course, be discontinued.

## DISEASES OF THE INTESTINES

By J. ARNOLD BARGEN, M.D.

**REGIONAL ENTERITIS.**—Although localized, inflammatory disease of the small intestine has occurred sporadically in the practice of many clinicians and surgeons before 1932, it was not until Crohn, Ginzburg, Leon and Oppenheimer in that year reviewed a group of cases under the designation "distal or terminal ileitis" that this subject aroused general interest. Following Bargaen's discussion of Crohn's paper before the American Medical Association in New Orleans, the term "regional ileitis" crept into the literature as a designation for a local inflammatory disease of the small intestine. Crohn and his associates originally believed that the pathologic changes in this clinical entity were confined to the terminal segments of the ileum. Hence, they had called it "terminal ileitis." It has since been demonstrated by many men that a pathologic process, identical with that which occurs in the terminal portion of the ileum, may occur in any part of the small intestine.

**Etiology.**—That the process is an infectious disease, primarily of the small intestine, seems to be generally agreed. The nature of the organism that causes this infection is at present undetermined. In many respects the condition resembles the lesion of chronic ulcerative colitis and in some cases a streptococcus-producing lesion has been found in the intestine of animals. Some have suggested that the initial lesion might be appendiceal in origin. There is some evidence to support this suggestion,

as the clinical history frequently reveals that an appendectomy had been performed before the onset of the symptoms of regional ileitis. Some writers object to this theory and believe that the appendix was removed because of an erroneous diagnosis. In many cases the lesion at first was thought to be tuberculous. No satisfactory evidence for this belief is at hand. T. E. Jones and R. J. Byrne (*S. Clin. North America* 15: 1035 (Aug.) 1935) made the significant observation that in all cases of recurrent appendicitis the terminal portion of the ileum should be carefully examined at the time of exploration.

**Clinical and Pathologic Features.**—Although regional inflammatory disease of the small intestine is now generally considered as an entity, it probably would be wise to think of it only as a clinical entity and not as a pathologic one. K. A. Meyer and P. A. Rosi (*Ibid.* 15: 697 (June) 1935), in an excellent review of the subject, have particularly emphasized this. They also have described phases of this infection. The disease was acute in 4 cases. In 3 cases in which the disease was acute, spontaneous resolution occurred; stenosis occurred in the fourth case in this group. In 4 cases the disease was chronic when the patients were first examined. The observations of these authors coincide with those of other careful observers of this condition. (J. A. Bargaen and C. F. Dixon: *Proc. Staff Meet., Mayo Clin.* 10: 814 (Dec. 18) 1935; J. Groen and A. W. M. Pompen: *Geneesk. bl. n. klin.*

en lab. v. d. prakt. 33:169, 1935; F. G. Connell: Am. J. Digest. Dis. and Nutrition 3:438 (Aug.) 1936). J. G. Probststein and G. E. Grunenfeld (Ann. Surg. 103:273 (Feb.) 1936) reported 3 cases of acute regional and intramural inflammation of the terminal portion of the ileum in which the patients recovered after laparotomy without resection of the diseased segment of bowel. The most exhaustive study of this condition probably is that of H. Koster, L. P. Kasman and W. Sheinfeld (Arch. Surg. 32:789 (May) 1936) who reviewed 17 cases observed personally and 100 cases which they collected from the literature. They emphasized the importance of subdividing the lesions into the following types: (1) early lesions, (2) moderately advanced but not obstructive lesions, and (3) advanced lesions associated with stenosis or fistulas. They included instances of enterocolitis in their cases and emphasized the close similarity of all these cases of regional, inflammatory disease of the intestine.

In general, the ages of patients afflicted with this disease are those at which chronic inflammatory disease usually afflicts the human body. In most of the cases the disease occurs in early adult life. The condition has been recognized among children. In most cases the patients have been ill for years before the diagnosis was established. The symptoms run a fairly constant and rather progressive course. Rarely is a case of regional ileitis seen in which the patient has been ill for less than 1 year previous to examination. Exploratory laparotomy very frequently has been performed because of a diagnosis of appendicitis. It is interesting in this connection to note that the surgeon often had described an abnormal condition of the ileum at the time of appendectomy.

One of the most constant symptoms in these cases is *pain*. It was the predom-

inant symptom in 16 of the 18 cases reported in 1934 by Brown, Borgen and Weber. The pain was described by such terms as "cramp-like," "colicky," "knife-like," "gripping," "obstructive," "sickening," "to and-fro colic." In most of the cases in which the lesion was situated in the ileum the pain was localized to the right lower abdominal quadrant, but in some cases it was situated to the left of the umbilicus, around the umbilicus, in the lower part of the abdomen, and in one case it was described as extending from the gall-bladder to the region of the appendix. In those cases in which the lesion was localized to the jejunum, the pain was said to occur just above the umbilicus. The inconstant relief from pain by various and sundry methods seemed rather characteristic. Six of the 18 patients had rather marked *diarrhea*, 3 of these had constant diarrhea, and 3 of them had diarrhea intermittently. It is interesting to note that in 6 cases the resected portion of the bowel contained ulcerative lesions of the mucosa. Furthermore, in 4 of these 6 cases there was involvement of the cecum, in 1 there was involvement of the terminal portion of the ileum alone, and in 6 cases there was extensive involvement of the jejunum. The diarrhea was of the loose, watery type. It was associated with much urgency and cramping, but no visible blood was present in the stools. In half of the cases *vomiting* was a distressing symptom; in several cases it was the most annoying symptom. The situation and character of the lesion seemed to be a factor in the production of the vomiting. In the 3 cases in which there were jejunal lesions, it was a very striking symptom. The vomiting did not seem to be that of impending obstruction, but was more intermittent and only partial loss of food and drink occurred. *Fever* was a common symptom. In some



cases recurrent episodes of fever occurred. While the fever reached 104 degrees (40° C.), the usual range was between 100 degrees and 101 degrees (37.7° and 38.3°C.), with alternating periods of freedom from fever.

*Loss of weight* is a striking symptom. Sometimes this is rapid and is cause for great anxiety. *Objective signs of the infection*, such as abdominal fistulas, moderate to marked secondary anemia, moderate leukocytosis, and emaciation may occur. If the patient is a woman, the lesion may be palpable as an extensive movable tube behind the uterus, in the vaginal cul-de-sac. When such is the case, the condition is very striking in that such a thick tube can be pushed out of the cul-de-sac by bimanual palpation and will promptly return to its former position. A sausage-shaped tender mass is not infrequently palpated in the lower right abdominal segment. The inflammatory process is usually sharply localized to a segment of the intestine. It involves all layers of the intestinal wall and is associated with hypertrophy. Its similarity to a stiff rubber tube or to chronic ulcerative colitis is at once apparent. Enlarged lymph nodes will be encountered along the mesentery. K. A. Meyer and P. A. Rosi (Surg. Gynec. and Obst. 62:977 (June) 1936) have described the pathologic changes of the chronic phase as a hyperplasia of the intestinal wall by a nonspecific inflammatory granulation tissue containing granulomas, foreign body giant cells and an excessive amount of connective tissue. Deep longitudinal ulcers and subacute inflammatory lesions have been observed in some cases and hypertrophic and stenotic lesions have occurred in others. At times, the linear ulcers have penetrated the intestinal wall and sinuses have resulted. H. L. Bockus and W. E. Lee (Ann. Surg. 102:412 (Sept.) 1935) have noted the close similarity of chronic

ulcerative colitis and regional ileitis. They, J. H. Musick (J. Oklahoma M. A. 28:95 (Mar.) 1935) and others, too, have emphasized that although the lesion has a predilection for the terminal portion of the ileum, pathologic processes of a similar nature may occur anywhere in the intestine.

**X-ray Studies.**—The pathologic nature of this disease predicts its x-ray manifestations. These are practically the same as those exhibited by the large intestine when it is similarly involved. There will be evidence of mural thickening, consequent narrowing of the lumen, stiffening and shortening of the involved portion, and mucosal destruction. Associated with these anatomic changes is a more or less pronounced hypermotility. To discover these changes, a properly conducted x-ray examination of the small intestine is important. Such an examination demands close scrutiny of intestinal segments by multiple x-ray observations of the descending opaque meal and careful investigation of the terminal portion of the ileum while it has been distended by reflux of the opaque enema through the ileocecal orifice. Careful examination with the barium enema as well as with the barium meal is often indicated, and narrowing of the lumen and shortening of the involved segments will usually be observed rather readily. Mucosal destruction will be seen by changes in internal relief.

**Treatment.**—A few years ago surgical treatment was advised in all or nearly all of the cases. Such studies as those of Probst and Gruenfeld, Meyer and Rosi, Koster, Kasman and Sheinfeld, and recent observation of cases at The Mayo Clinic will emphasize the importance of a very detailed study of these cases. Medical measures have included **sunbaths, general supportive and dietetic measures**, and the administra-

tion of a **vaccine** prepared from the bacteria isolated from the intestinal lesions of these patients. In most cases, however, it can be said that, at this time, **surgical treatment** is the treatment of choice. Short-circuiting operation, including ileocolostomy and ileostomy, frequently have been performed. Later, resection of the involved segment has been performed. There are those, including Crohn and Berg, I. Snapper, A. W. M. Pompen and J. Groen (*Ann. de Méd.* 39:5 (Jan.) 1936), Koster, Kasman and Sheinfeld, who have felt that eradication of the lesion would be the only procedure that would offer a clinical cure. However, when it is considered that in a fair number of cases complete recession of the lesion occurs after a short-circuiting procedure alone, and the 11 cases of C. G. Mixter (*Ann. Surg.* 102:674 (Oct.) 1935) are recalled in which operative treatment was accompanied by a mortality of 36 per cent., it may be decided that less radical procedures should be employed whenever possible.

**Summary.**—Regional ileitis is a localized, inflammatory disease of the small intestine which has a tendency to progression. Granulomas, fistulas, and obstruction are likely to occur (M. Paulson: *Am. J. Digest. Dis. and Nutrition* 3:430 (Aug.) 1936; J. O. Hagen: *Minnesota Med.* 19:766 (Dec.) 1936; B. B. Crohn: *Am. J. Digest. Dis. and Nutrition* 3:736 (Dec.) 1936). The etiology is not entirely clear, but early diagnosis cannot be too strongly urged. Eradication of the lesion whether by medical or surgical means seems to be the treatment of choice.

**ILEOCOLITIS (REGIONAL ENTERITIS AND ENTEROCOLITIS).**—The early descriptions of regional ileitis suggested that this localized hyperplastic inflammatory lesion involved only segments of the distal portion

of the ileum. Subsequent reports by many observers have demonstrated clearly that similar inflammations may involve any portion of the small intestine as well as the proximal portion of the colon. Sporadic reports of localized intestinal inflammatory disease have appeared for many years. The reports have been that lesions were nontuberculous and yet non-specific as far as etiology was concerned. Personal observations and those of many others, notably K. A. Meyer and P. A. Rosi (*Surg., Gynec. and Obst.* 62:977 (June) 1936); A. J. Rosenblate, A. A. Goldsmith and A. A. Strauss (*J. A. M. A.* 106:1797 (May 23) 1936); H. Koster, L. P. Kasman and W. Sheinfeld (*Arch. Surg.* 32:789 (May) 1936); I. H. Erb and A. W. Farmer (*Surg. Gynec. and Obst.* 61:6 (July) 1935); H. L. Bockus and W. E. Lee (*Ann. Surg.* 102:412 (Sept.) 1935); A. Castellanos (*Bol. Soc. cubana de pediat.* 8:258 (May) 1936); V. H. Musick (*J. Oklahoma M. A.* 29:280 (Aug.) 1936), indicate that the lesions of the various intestinal segments are pathologically identical. Furthermore, they represent a progressive disease passing through various phases, from an acute inflammation to chronic hyperplastic enteritis. At times there are sequelae, such as mesenteric abscesses and fecal fistulas, and at other times spontaneous resolution occurs. The symptoms, too, will change with various phases of the pathologic process and may be progressive and become increasingly more distressing and more difficult to control. Such experiences would suggest that it is probably unwise to consider "regional ileitis" and "ileocolitis" under separate headings.

A man, aged 25, came to the clinic on July 11, 1935, because of recurrent diarrhea which had been present for 1 year. During the previous winter he had been much better and loose stools had occurred only occasionally. By March, 1935, the diarrhea had become severe and had been associated with abdominal

cramps, marked fatigue, and loss of weight. He had not seen blood in the stools but from that time until his admission to the clinic he had averaged 10 to 12 stools a day. The diarrhea had been associated with much tenesmus after meals. Occasionally, he had vomited. With the exception of a moderate anemia and obvious loss of weight, the only significant



Fig. 1.—Ulcerative disease of distal portion of ileum as observed July, 1935.

feature was a narrowing and fuzziness of a distal segment of ileum in the roentgenogram (Fig. 1). Symptomatic treatment produced slight improvement and the patient was allowed to return home. He returned to the clinic on November 13th. His condition had become worse after some initial improvement. X-ray examination of the colon on November 19th revealed an extensive lesion which involved a large segment of the ileum and the transverse colon and right half of the colon (Fig. 2). He was acutely ill and operation seemed contraindicated at that time. The lesion was advanced by January 14, 1936 (Fig. 3). By January 22nd there had been sufficient general improvement to warrant an exploratory laparotomy. This revealed lesions of the right half of the colon, the transverse colon, and the terminal ileum. Ileosigmoidostomy was performed and the involved segments of the colon and 8 inches (20.3 cm.) of the ileum were removed. There was some improvement but later there was further recurrence of

trouble. When the patient was examined in July, 1936, it was found that the lesion had extended down the descending colon and had involved the rectum. His condition has not been satisfactory for the type of operation which would seem necessary for eradication of this disease. Symptomatic measures have been undertaken. This case illustrates how the condition may begin in the ileum, present the typical picture of regional ileitis, extend in a retrograde fashion, and finally involve the entire colon.

**Etiology.**—Although the exact cause of this condition has not been determined, its clinical course and pathologic changes suggest a close similarity between it and chronic ulcerative colitis of the streptococcic type. Moreover, in some instances, a streptococcus closely resembling the organism isolated in

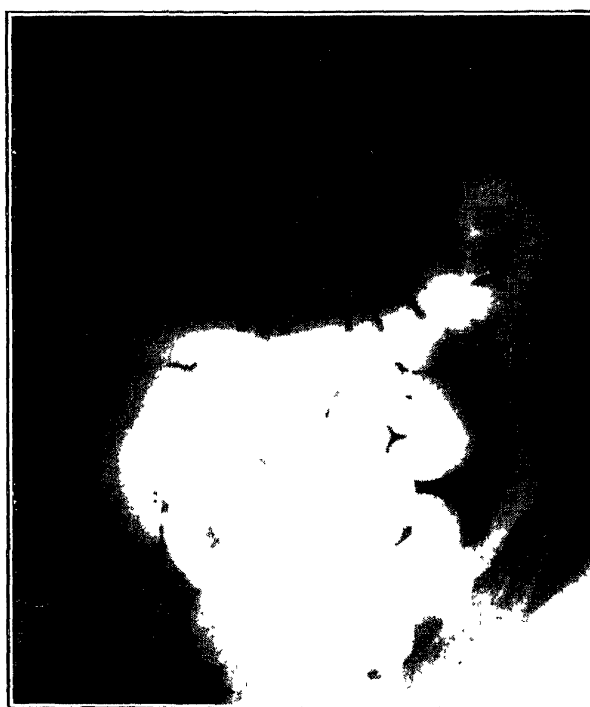


Fig. 2.—Involvement of distal portion of ileum, ascending and hepatic flexures of colon, and a large section of descending colon, as observed November, 1935.

chronic ulcerative colitis has been obtained from the walls of freshly excised specimens of small intestine. Attempts have been made by (J. Felsen (New

York State J. Med. 35:576 (June 1) 1935) to ascribe these lesions to strains of dysentery bacilli. He suggested that chronic ulcerative colitis, regional ileitis, and ileocolitis are all phases of bacillary dysentery. Experimental confirmation of this theory is lacking. The question



Fig. 3.—Further advance of disease, as observed January, 1936.

further arises, whether or not the enteritis of Breslau, described by L. Seitz (Jahrb. f. Kinderh. 145:31 (July) 1935) or the epidemic enteritis described by L. Paré (Union méd. du Canada 64:1137 (Sept.) 1935) may not be phases of this infection or eventuate in this infection.

**Pathologic Changes.**—As knowledge of this condition accumulates it becomes more and more apparent that it is a progressive disease which passes through the phases of acute to chronic inflammation. Paralleling symptomatic evidence of chronicity, there occurs a somewhat sharply localized inflammatory thickening and hypertrophy of the intestine. The involved intestine is covered here

and there by an inflammatory exudate which closely resembles the lesion of chronic ulcerative colitis. When the abdomen is opened, the large mesenteric lymph nodes along the involved segment of bowel are encountered. Many observers have likened the involved segment of bowel to a "stiff rubber hose" and have noted mucosal ulceration. Microscopic sections will show diffuse involvement and vascular thrombosis similar to that seen in progressive chronic ulcerative colitis. Foreign body giant cells are not uncommon in the wall of such a bowel. Evidence of tuberculosis has at times been suggested but not confirmed.

**Treatment.** In the main, the guidance for therapy outlined for regional ileitis applies to this condition. The treatment should vary with the stage of the disease, *viz.*, the early lesion, the moderately advanced one, and the advanced lesion, which is associated with stenosis or fistula. It is not infrequently difficult to evaluate the proper time for surgical intervention. Some patients have responded to medical management with complete recession of the infectious process. Such a medical régime should be somewhat similar to the program outlined for use in the average case of chronic ulcerative colitis. E. Lauda (Wien. klin. Wchnschr. 49:53 (Jan. 10) 1936) offered a very satisfactory program of dietary management as one of the therapeutic measures in these cases. His diet in the main is high in protein and calories and low in residue. The lesion at times is rapidly progressive and in some instances operation may have been delayed too long. Sometimes the lesion is so extensive when first observed that ileocolostomy and resection are formidable procedures. At The Mayo Clinic, cases have been observed in which there was involvement of long stretches of ileum and the proximal portion of the colon. In one case, most

of the jejunum was involved in a massive inflammatory process. These advanced lesions confirm the suggestion that **surgical resection** is probably the treatment of choice. On the other hand, the risk of this operation is considerable. Some patients improve under a **medical régime** and hence in the cases of early and uncomplicated involvement some form of medical program may be tried.

#### **DIVERTICULOSIS AND DIVERTICULITIS OF COLON.**—

**Definition, Incidence, Age, Sex, Bodily Build.**—Diverticula of the colon are fairly common and usually are of the acquired type. They appear as pear-shaped or retort-shaped sacculations connected to the lumen of the intestine. When simple diverticula free from inflammation are found, the term "diverticulosis" is commonly used to describe them. Broadly speaking, the term "diverticulitis" refers to a complication of diverticulosis, *viz.*, the inflammatory phase, which may have various sequelæ. The first reference to diverticulosis probably was that by Littre, in 1700. H. C. Ochsner and J. A. Barger (Ann. Int. Med. 9:282 (Sept.) 1935; Illinois M. J. 69:45 (Jan.) 1936) have made a comprehensive review of the historical features of this condition. This condition was discovered to affect only 0.4 per cent. of the patients who registered at The Mayo Clinic in 1933. This percentage is undoubtedly too low, as indicated by the fact that diverticula were discovered in 6.9 per cent. of 447 cases in which patients came to necropsy in the same period and in 7 per cent. of 2747 cases in which x-ray examination of the colon was performed in the same period. By a most comprehensive review of the condition K. Lunding (Acta med. Scandinav. (Supp.) 72:1, 1935) determined that 5 per cent. of patients who were subjected to x-ray examination because of intestinal symptoms had diver-

ticula of the colon. In 11 per cent. of the cases of diverticulosis observed at the clinic in 1933, diverticulitis was present at the time of examination, and in 13 per cent. of the cases the history was suggestive of previous attacks of diverticulitis. The situation of the diverticula in these cases is shown in TABLE I. Diverticulosis was found to affect males slightly more often than it affected females, but in the cases in which diverticulitis was present, the males exceed the females in the ratio of 2.75:1. Diverticulosis rarely occurs before the age of 30 years. After this age, the incidence of diverticulosis increases slowly in each half decade until between the fifty-fifth and fifty-ninth years, when the peak of incidence for each sex occurs. After this, its progressive incidence decreases. Much has been written about the relation of obesity to diverticulosis. Statistically, diverticulosis is as common among lean individuals as it is among obese individuals S. Barling (Birmingham M. Rev. 11:12 (Mar.) 1936) and J. Morley (Liverpool Med. Chir. (Sept. 2) 43:67, 1935).

**Etiology.**—Congenital and acquired diverticula of the colon will be found described in the literature. The former are undoubtedly very rare. When considering the latter, investigators repeatedly have asked whether they were traction or pulsion diverticula. Various investigators have attempted to substantiate their opinions on this point. Klebs found all the strata of the intestinal wall in some diverticula and the diverticula were localized to the places where the vessels penetrated the intestinal wall. He theorized that the mesentery grew faster than the vessels, which caused a stretching of the intestinal wall and hence produced traction. Most authors are of the opinion that diverticula are of the pulsion type and explain them on the basis of pressure from the

TABLE I

| <i>Uncomplicated Diverticulosis</i><br>(72.60 Per Cent. of Total Cases)                  |        |           |
|--|--------|-----------|
| Situation  | Number | Per Cent. |
| Sigmoid flexure .....  | 62     | 41.1      |
| Sigmoid flexure and descending<br>colon .....  | 26     | 17.2      |
| Left half of colon.....  | 28     | 18.5      |
| Entire colon .....   | 19     | 12.6      |
| Ascending colon .....  | 3      | 2.0       |
| Hepatic flexure .....  | 2      | 1.3       |
| Ascending colon and sigmoid<br>flexure .....   | 2      | 1.3       |
| Cecum .....  | 2      | 1.3       |
| Splenic flexure .....  | 2      | 1.3       |
| Transverse colon .....   | 1      | .7        |
| Transverse colon and sigmoid<br>flexure .....  | 1      | .7        |
| Left half of colon and cecum...  | 1      | .7        |
| Right half of colon .....  | 1      | .7        |
| Right half of colon and sigmoid<br>flexure .....   | 1      | .7        |
| <i>Diverticulosis With History of Diverticulitis</i><br>(12.98 Per Cent. of Total Cases) |        |           |
| Situation  | Number | Per Cent. |
| Sigmoid flexure .....  | 11     | 40.7      |
| Sigmoid flexure and descending<br>colon .....  | 10     | 37.0      |
| Entire colon .....   | 4      | 14.8      |
| Left half of colon.....  | 2      | 7.4       |
| Total incidence of diverticulosis 85.58 per<br>cent. of total cases.                     |        |           |
| <i>Uncomplicated Diverticulitis</i><br>(11.06 Per Cent. of Total Cases)                  |        |           |
| Situation  | Number | Per Cent. |
| Sigmoid flexure .....  | 19     | 82.6      |
| Sigmoid flexure and descending<br>colon .....  | 2      | 8.7       |
| Descending colon .....   | 2      | 8.7       |
| <i>Diverticulitis With Perforation</i><br>(2.40 Per Cent. of Total Cases)                |        |           |
| Situation  | Number | Per Cent. |
| Sigmoid flexure .....  | 4      | 80.0      |
| Sigmoid flexure and descending<br>colon .....  | 1      | 20.0      |
| <i>Diverticulitis With Obstruction</i><br>(0.96 Per Cent. of Total Cases)                |        |           |
| Situation  | Number | Per Cent. |
| Sigmoid flexure .....  | 2      | 100.0     |
| Total incidence of diverticulitis 14.42 per<br>cent. of total cases.                     |        |           |

contents of the intestine, changed conditions of the intestinal wall associated with an increased width of the vascular gaps, and a hereditary predisposition. Graser was able to demonstrate innumerable microscopic herniations of the mucous membrane at the points at which vessels entered the intestinal wall. With advancing years the reduced power of resistance of the mellow tissue around the vessels, disappearance of the mucosal vessels in the intestinal wall, a decrease and weakening of the submucosal and interfascial and connective tissue, coupled with a congenital tendency, may all be factors in the production of diverticulosis. Spriggs and his associates have looked for the cause of diverticula in inflammatory changes of the intestinal membrane. They have described a pre-diverticular state characterized roentgenologically by a notched, palisade-like outer contour of the intestinal wall. Between this notched contour, other non-dilatable places have been demonstrated, the condition occurring from transition stages to fully developed diverticula.

These factors may all play a part in the formation of diverticula, but diverticula are herniations of the mucous membrane through a gap in the musculature, and their age incidence would strongly suggest that they are merely changes which occur during old age and are no more serious than wrinkles in the face or gray hair, unless complications develop.

**Symptoms.**—It is not certain that any symptoms can be ascribed to diverticulosis. That 40 per cent. of individuals who have diverticulosis of the sigmoid colon have constipation and only 8 per cent. have diarrhea may not be significant. Flatulence occurs in approximately 20 per cent. of cases and abdominal pain and discomfort occur in a similar number. When pain occurs it is localized to the lower part of the abdomen and

varies from a sense of fullness to cramping. A few patients have noted a narrowing of the diameter of the stool. Some speak of an irritable intestine. In the cases in which diverticula occur throughout the entire intestine or in definite segments of the intestine, 56 per cent. of the patients complain of constipation.

The situation is different in the cases of diverticulitis observed at the clinic. In these cases 63 per cent. of patients complained of irregularity of bowel movements. In 27 per cent. of these cases there had been some diarrhea and in 36 per cent. there had been constipation. All the patients had had previous attacks of pain and 36 per cent. complained of abdominal pain at the time of examination, although there frequently was no evidence of diverticulitis at that time. The pain is localized in the left lower quadrant of the abdomen; it is dull in some cases and cramping in others, and is relieved to a large extent by bowel movements. Flatulence occurs occasionally. Pain occurs in 89 per cent. of the cases in which diverticulitis is not associated with perforation or other evidence of peridiverticulitis. There is a variable degree of urgency of bowel movements and the pain frequently is relieved by bowel movement. Constipation occurs in 58 per cent. of cases. Rectal bleeding occurs rarely. All the patients who have perforative diverticulitis of the sigmoid colon have pain which is localized in the left lower quadrant abdomen, is cramping in character, is accompanied by fever, and in half the cases is also accompanied by chills. The cramps may be relieved by bowel movements and sometimes by urination. Half of the patients complain of urinary frequency and burning. Occasionally, intestinal obstruction occurs.

**Objective Examination and Pathologic Changes.**—The physical examination of patients who have diver-

ticulosis does not reveal any changes that can be attributed to the existence of this condition. The same can be said of the examination of those who previously have had diverticulitis who have only diverticulosis at the time of examination. Consequently, the importance of subjective investigations is at once apparent. It has been found that when diverticula are multiple, they usually range themselves parallel to the longitudinal axis of the intestine, either close to the edge of the mesentery or at the site at which the appendices epiploicæ open. Their place of breaking through into the tunica muscularis is at the attachment of the appendices epiploicæ. Their shape will usually be that of a retort or pear. Although longitudinal muscular fibers may be found over the whole of the diverticulum, circular muscle fibers may be found to extend only a short distance down the neck of the diverticulum. Hansmann counted 400 diverticula in a man, aged 85 years; the largest of these was as big as a dove's egg. Fecal masses accumulating in such sacs may result in irritation and infection. With the inflammation, reaction which follows the secondary changes of diverticulitis will result. Because these diverticula most frequently occur in the sigmoid colon, their openings into the intestinal lumen can frequently be visualized through the sigmoidoscope. Hence, this becomes the first important method of diagnosis. Since the diverticula may occur in any portion of the large intestine, the most reliable method for demonstration will be an x-ray examination. The barium enema, administered under roentgenoscopic control, will demonstrate the diverticula as saccular outpouchings of the intestine. The x-ray appearance will be in striking contrast to that of polyposis (C. J. Marshall: Proc. Roy. Soc. Med. 29:339 (Feb.) 1936; J. Masson: Rev. méd. de la Suisse rom. 56:154

(Mar. 10) 1936; A. W. Erskine: J. Iowa M. Soc. 26:255 (May) 1936; G. Bignami: Arch. di radiol. 10:517, 1935; C. C. Underwood: J. Kansas M. Soc. 36:488 (Dec.) 1935; W. R. Jones: Minnesota Med. 18:319 (May) 1935). In diverticulosis there will be projections from the lumen and in polyposis the projections will be into the lumen. When diverticulitis complicates diverticulosis, the increased irritation and narrowing of the lumen present striking and characteristic features. By the combined use of x-ray and proctoscopic examination, diverticulosis can practically always be detected and in most cases diverticulitis can be distinguished from other intestinal lesions. The opinion of the roentgenologist may be given greater weight than that of the clinician or surgeon who has actually examined the lesion. There is nothing diagnostic about the stools of a patient who has diverticulosis or diverticulitis. Lunding has considered the importance of the catalase test to distinguish diverticulitis from diverticulosis.

**Treatment and Prognosis.**—The best *treatment* for diverticulosis consists of the avoidance of constipation and irritation; this is best accomplished by the use of a diet which is bland and nonconstipating and which is free from residue. **Liquid petrolatum** should be administered orally as a lubricant.

It is our practice (at the Clinic) to administer **atropine** or **tincture of belladonna** to help relieve and to avoid spasm. Diverticulitis always is associated with some peridiverticulitis, and the milder degrees of this condition do not materially alter the outlook for the patient. The occurrence of the more serious complications, such as abscesses with or without perforation, fistulas, peritonitis, and obstruction, which cannot be relieved by medical measures, constitute a clear indication for conservative operation. Once such compli-

cations occur, the future is fraught with danger unless the intestine can be resected. However, some patients who had complications which demanded **colostomy** have recovered; the colonic stoma has been closed and no further trouble has been experienced.

The *prognosis* of simple diverticulosis is good, although some likelihood of inflammation exists. The prognosis of uncomplicated diverticulitis is rather good; most patients can be relieved by the medical measures which have been described previously.

**POLYPOSIS OF LARGE INTESTINE.**—*Pseudopolyposis* is well illustrated by Virchow's "polyposis colitis cystica," which seems to have been the sequel of some inflammatory disease. This condition has been present in about 10 per cent. of a series of 1000 cases of chronic ulcerative colitis observed at The Mayo Clinic. In these cases the so called "inflammatory polyps" occurred apparently as a result of great damage to the intestinal wall and destruction of mucous membrane, so that islets and studs of the mucous membrane remain. When healing took place these islets projected above the remainder of the mucous membrane. Pulling and tugging of feces and the inclusion of mucus and inflammatory material in the projecting portion resulted in polypoid lesions. These have been known to grow to considerable size and adenomatous change may develop in these tags. They present a clinical picture entirely different from the condition described as disseminated polyposis by C. W. Mayo and E. G. Wakefield (J. A. M. A. 107:342 (Aug. 1) 1936). The latter condition has been designated "adenomatosis," "multiple adenomatous polyposis," and "congenital or adolescent polyposis." There is no evidence that a child was ever born with such a disseminated polyposis, but the condition has been observed in a child



2½ years of age. There is a distinct suggestion of a hereditary tendency. Furthermore, there are records of families in which 4 of 6 children have been afflicted with this type of polyposis and in one particular instance the mother had had a similar condition. Symptoms usually occur early in life. A review of some of these cases has suggested that a Mendelian dominant is present. In addition to this disseminated or adenomatous type of polyposis, single polyps or a few polyps may occur late in life. They may not be noted by the patient until bleeding or some other intestinal difficulty is noted. Some knowledge of the frequency of this condition may be gathered from the fact that in the Section on Proctology at The Mayo Clinic 4 per cent. of patients examined were found to have one or more polyps that could be visualized with the sigmoidoscope. Only 0.04 per cent. of these patients had disseminated polyposis. These studies agree essentially with those of L. J. Bernard (M. Bull. Vet. Admin. 12:389 (Apr.) 1936), R. R. von Oppolzer (Arch. F. klin. Chir. 182:152, 1935) and others. It is noteworthy that, whereas the average age of the patient who has multiple adenomatous polyposis is less than 40 years, that of the individuals who have single polyps is likely to be more than 50 years. In the 19 cases of disseminated polyposis reviewed by Mayo and Wakefield, the average age of the patients was 29 years. It will be seen, therefore, that pseudopolyposis and disseminated adenomatous polyposis occur early in life and hence present an important differential diagnostic problem. It is generally agreed that adenomatous polyps may be considered as forerunners of carcinoma. Notable in this respect is the study by Fitzgibbon, Grattan and Rankin in 1931 and in 1935 by F. W. Rankin (Ann. Surg. 102:707 (Oct.) 1935). It has

been estimated by Wesson and Barger that carcinoma will develop in nearly 100 per cent. of cases of multiple adenomatosis or disseminated polyposis. On the other hand, single and multiple carcinomas occurred in 2.5 per cent. of a large group of cases of chronic ulcerative colitis. Furthermore, it was found that carcinoma developed in 25 per cent. of the cases in which chronic ulcerative colitis was associated with polyposis of the colon. Brust and Buie have pointed out that the incidence of carcinoma in single adenomatous polyps of the rectum is about 5 per cent. The importance of distinguishing the various types of polyps therefore becomes apparent. An actual diagnosis of the type of polyp will do much toward expressing a favorable or unfavorable prognosis.

The *clinical course* of polyps varies according to the type and extent of polyp present. Polyps may develop during the observation of a case of chronic ulcerative colitis. They are obviously of the pseudopolypoid type. On the other hand, if an individual is first seen when he has slight rectal bleeding or other intestinal irritation, and if polyps are found, it is most important to obtain a very complete and detailed history of any previous intestinal disturbances. In a case of disseminated polyposis, the first symptom may be slight bleeding and even then one or more carcinomas may be observed. Frequently, the types of polyps may be differentiated by digital examination of the rectum alone. In the case of pseudopolyps, the involved segments of intestine will be stiff, narrow and tube-like. Irregular disseminated mucosal protuberance will be present and at times rather large projections may occur. In the case of disseminated polyposis, the wall of the bowel will be soft and flexible and the lining will be studded with innumerable projections of similar size which often impart the

feeling that the finger is being passed over a rubber scrub brush. Single polyps may have pedicles and dumb-bell-shaped ends which project into the lumen of the intestine. The proctoscopic examination is probably the most important single diagnostic aid in studying the polyps within its reach. Finally, in cases in which polyps appear in segments above the rectum, x-ray studies are invaluable and the only reliable means of diagnosis. Such examination should be made by the double contrast method and the barium should be injected into the thoroughly cleansed colon. After the barium has been expelled, air is injected into the intestine under roentgenoscopic control and stereoscopic roentgenograms are made.

*Treatment* of polyposis implies **eradication** of the polyps. This may be done in several ways. **Fulguration** of the polyps in the region visible with the sigmoidoscope has become a very satisfactory method of treatment. However, in many cases there are polyps beyond the reach of this instrument. Various surgical maneuvers have been devised to eradicate these polyps. When there are a few polyps or just one polyp in a movable segment of bowel, **trans-colonic resection** is satisfactory. When the polyps are multiple and disseminated, removal of long segments of intestine may be necessary (J. A. Bargen and C. F. Dixon: Proc. Staff Meet. Mayo Clin. 10:648 (Oct. 9) 1935; E. S. Zelenskaya: Novy khir. arkhiv. 35:419, 1936; T. G. Nyström: Finska läk-sällsk. handl. 77:619 (Oct.) 1935). In many of these cases **ileostomy**, which may prove to be a permanent affair, followed by single or multiple stage **colectomy**, may be necessary. At times, **ileosigmoidostomy** is possible and **fulguration** of the polyps below the ileosigmoid stoma and **resection** of the colon proximal to the stoma may be employed.

The chief consideration in all these cases should be the eradication of the polyps at the least risk to the patient. This then brings up the question of treatment of the polyps which occur as a sequel of chronic ulcerative colitis. Since most of them are not adenomatous in character, conservative treatment directed toward relief of the colitis should always be undertaken. If polyps grow even when the symptoms subside and the colitis heals, then radical operation occasionally may be necessary. Most of these polyps can be controlled by medical measures. This is the only group of polyps about which this can be said and these are not true polyps. The best treatment of all other polyps is **removal**.

**ULCERATIVE COLITIS.—Complications.** The complications that occurred in 1500 cases of chronic ulcerative colitis are shown in TABLE I. In this group of cases approximately 15 per cent. of the patients had complications.

TABLE I  
*Complications in 1500 Cases of Chronic Ulcerative Colitis.*

| Complication                                       | Incidence |
|--|-----------|
| Polyposis.....                                     | 130       |
| Stricture of large intestine.....                  | 110       |
| Arthritis.....                                     | 60        |
| Perirectal abscess.....                            | 50        |
| Cutaneous lesions.....                             | 42        |
| Malignant disease.....                             | 31        |
| Perforation of large intestine.....                | 30        |
| Renal insufficiency.....                           | 15        |
| Endocarditis.....                                  | 15        |
| Massive rectal hemorrhage<br>(exsanguinating)..... | 15        |
| Phlebitis.....                                     | 15        |
| Splenomegaly.....                                  | 14        |
| Ocular disease.....                                | 10        |
| Nutritional edema.....                             | 10        |
| Peripheral neuritis.....                           | 5         |
| Progressive arterial occlusion.....                | 3         |
| Multiple abscesses of liver.....                   | 2         |
| Tetany.....  | 1         |

**Prognosis.**—A very excellent evaluation of this phase of the subject was made by A. F. Hurst (Lancet 2:1194 (Nov. 23) 1935), who said: "A large majority of patients with chronic ulcerative colitis however severe, should recover eventually so completely that they are able to lead a life of normal activity. There is a great tendency to recurrence, but if each recurrence is treated promptly until all traces of disease have passed, the recurrences become milder and more infrequent until finally they cease." It is also interesting, as J. C. M. Brust and J. A. Borgen (Minnesota Med. 18:583 (Sept.) 1935) have shown, that in a general way the older the patient is, the less severe the colitis will be and the better will be the ultimate prognosis.

**Treatment.**—Probably the most complete consideration of this disease which has appeared recently is that by A. F. Hurst (Guy's Hosp. Rep. 85:317 (July) 1935; Brit. M. J. 1:320 (Feb. 15) 1936). That much misunderstanding about the nature of this disease still exists is well illustrated by the numerous attempts at treatment which are based on entirely different conceptions. In a review of existing types of colitis by H. N. S. Turner (Guy's Hosp. Gaz. 50:64 (Feb. 15) 1936), chronic ulcerative colitis was not even mentioned. In addition to the well-established program of treatment by **anticolitis streptococcus serum, vaccine, transfusion, diet** and their adjuncts now in common use, the following therapeutic suggestions should be mentioned.

B. Fornet (Klin. Wchnschr. 14:1859 (Dec. 28) 1935) advised the entral administration of **serum**. He reported 10 cases in which repeated intestinal instillation of 10 c.c. of serum in physiologic saline solution produced satisfactory results. E. J. Oesterlin, A. W. Johnson, J. Kinsey and T. Will-

ett (Wisconsin M. J. 34:538 (Aug.) 1935) reported similar success with the **antivirus treatment**. A. Winkelstein and C. Herschberger (Am. J. Digest. Dis. and Nutrition 2:408 (Sept.) 1935) have used **dysentery bacteriophage**. S. A. Portis (M. Clin. North America 18:1519 (Mar.) 1935) and many others have advocated the use of **antistreptococcic colitis serum**. A. Grumbach and A. Haemmerli (Arch. f. Verdauungskr. 59:52 (Feb.); 239 (Mar.) 1936) have reported very encouraging results with the use of **streptococcic vaccine** administered in increasing doses **by mouth**. During a recent visit to the Grumbach laboratory in Zurich, the writer reviewed 14 cases in which the patients had been treated in this manner. There had been one failure in this series of cases. **Calcium** and **parathyroid extract** still are used by a few men, notably B. Haskell and A. Cantarow (Am. J. M. Sc. 190:676 (Nov.) 1935) and E. W. Klinefelter (M. Rec. 141:573 (June 19) 1935). Several men, especially J. Rachet and A. Busson (Paris méd. 1:308 (Apr. 6) 1935; Arch. d. mal. de l'app. digestif. 25:743 (July) 1935) have emphasized the importance of **vitamins** in the diet. G. Hetényi (Orvosi hetil. 79:557 (May 18) 1935; Klin. Wchnschr. 14:1470 (Oct. 12) 1935) reported favorable effects from the intravenous administration of **cevitamic acid** in 7 cases.

**Alpha naphco jelly** has been used by E. L. Cartwright (Am. J. Digest. Dis. and Nutrition 3:70 (Mar.) 1936) and J. F. Montague (M. Rec. 143:101 (Feb. 5) 1936) has administered a buffered solution of **sodium citrate**. H. Kochs (München. med. Wchnschr. 82:1284 (Aug. 9) 1935) advocated the use of a pectin derivative (**sangostop**) for the treatment of *hemorrhages* of this disease as well as for the treatment of other types of internal hemorrhage. H.

Horster (Deutsche med. Wchnschr. 62: 19 (Jan. 3) 1936) has reported favorable effects from the injection of a substance prepared from the mucosa of the small intestine of pigs. This substance is called "**torantil.**" Furthermore, W. Schemensky (Ztschr. f. klin. Med. 128: 428, 1935) advocated the oral use of a **powder prepared from the colons of hogs.**

It may be significant that in the past 2 years 10 articles on the **surgical treatment** of some phases of chronic ulcerative colitis have appeared. It certainly is significant that in these articles many types of operation have been proposed. C. F. Dixon's (Minnesota Med. 19:33 (Jan.) 1936) critical evaluation of the place of surgical treatment in this disease is outstanding. I. C. McKittrick and R. H. Miller (Ann. Surg. 102:658 (Oct.) 1935) have made an excellent review of 143 cases in which surgical treatment was employed. They have attempted to evaluate *indications* for surgical intervention. The consensus of opinion seems to be that surgical treatment should be employed only in the presence of complications, such as fis-

tulas, obstruction, polyposis, neoplastic change, and in a few cases in which the disease seems impossible to control medically. Among the papers noteworthy in this respect should be mentioned those by R. B. Cattell (J. A. M. A. 104:104 (Jan. 12) 1935), D. P. MacGuire (Am. J. Surg. 29:199 (Aug.) 1935), S. M. Jordan and E. D. Kiefer (Tr. Gastro-Enterol. A. 36:61, 1933), H. H. Trout (Virginia M. Monthly 63:1 (Apr.) 1936), J. Flick (Ann. Surg. 103:638 (Apr.) 1936), E. W. Rankin (*Ibid.* 102:707 (Oct.) 1935), and J. A. Barger and C. F. Dixon (Arch. Surg. 30:854 (May) 1935). C. A. Kunath (*Ibid.* 32:302 (Feb.) 1936) has reviewed the time worn procedures, **appendicostomy** and **cecos-tomy**, but has suggested that his discussion offered a "transient opinion, and not a permanent policy." If a common understanding of the nature of this disease existed, many discussions such as some of those appearing in the current literature would not occur. McKittrick and Miller have given a very splendid evaluation of surgical procedures in this disease.

## CONSTIPATION

By JULIUS FRIEDENWALD, M.D., and SAMUEL MORRISON, M.D.

**Treatment.**—During the past year H. C. Trumble (Brit. J. Surg. 23:214 (July) 1935) has called attention to the **surgical treatment** of constipation. Regarding the selection of cases and the type of operation, Trumble describes 3 main groups. The *first group* is comprised of cases in which severe constipation is associated with gross dilatation of the colon. For this group the operation is radical and aims at the destruction of the greater part of the lumbar sympathetic supply to the colon. In the *second group*, which comprises cases

in which there is severe constipation associated with chilblains or "chilblain circulation" of the extremities, the operation consists of excision of both lumbar trunks below the first lumbar ganglion. Cases of extreme constipation, unresponsive to conservative measures and associated with other troubles, such as dysmenorrhea, neurasthenia, indigestion, and poor health generally, are placed in the *third group*. When other measures have failed, resection of portion of the hypogastric nerves may be tried in these cases. "It is hardly necessary to state,"

writes Trumble, "that no patient should be subjected to operation until conservative measures have been thoroughly tried out and have failed. On the other hand, intractable constipation may make a person very miserable and an operation holding out some hope of relief should not be denied him when all other measures fail to give relief."

R. Flynn (M. J. Australia 1:613 (May 2) 1936) reports a case of severe constipation which was relieved by a **bilateral ramisection**, and J. W. Hinton (Ann. surg. 103:145 (Jan.) 1936) performed a **presacral sympathectomy** on a 28-year-old patient with obstinate constipation, who was relieved for 2 years by the operation, after which there was a slight recurrence. Among other reports is that of C. Otero (Cir. y. cirujanos 3:127 (June-Aug.) 1935) who reports on **rectocolonic sympathectomy** in cases of severe constipation. S. J. Stabins, J. J. Morton and W. S. M. Scott (Am. J. Surg. 27:107 (Jan.) 1935) have used *spinal anesthesia as a preoperative test* to determine whether **sympathectomy** would be of benefit.

*Spastic constipation in children* is discussed by A. W. Fellows (Maine M. J. 27:105 (May) 1936). In brief, he advises no laxatives, but rather the use of **belladonna**, which he considers a specific. In addition, **plenty of water** and no bran or allied rough residue foods are prescribed. Occasionally he finds **plain petrolagar** a very useful adjunct to the treatment, primarily because it prevents drying of the stool. F. H. Lancaster (South. M. J. 28:851 (Sept.) 1935) discusses the importance of **habit training** in the infant and especially **systematic effort** as the child grows older. Good habits in mastication of food, in eating time, in play, and outdoor exercise are taken up in detail.

Physical therapeutic measures in constipation are discussed by W. S. Horn (Arch. Phys. Therapy 17:225 (Apr.) 1936). He believes that the rational treatment of *atonic constipation* is, first, reduction of the amount of work required of the colon, and second, the strengthening of the muscles that must do the work. As a simple method of accomplishing both these ends he advises the sensible progressive use of **graduated rectal dilators** carefully followed up. R. Kovacs (Rev. Gastroenterol. 2:302 (Dec.) 1935) reports that physical measures offer a valuable aid in the constitutional as well as in the local treatment of chronic constipation, especially the atonic type. In *atonic constipation* general and local stimulation, derived from **massage**, **low frequency currents** and **exercise**, are indicated; whereas in *spastic constipation*, general nervous relaxation and local sedation will prove most effectual and this is best obtained in the form of **diathermy**. **Electrotherapy** is also discussed by J. Amiot (Rev. d'actinol. 11:406 (Sept.-Oct.) 1935) and by H. Tewes (München. med. Wchnschr. 83:142 (Jan. 24) 1936).

F. P. Weber (Practitioner 135:229 (Aug.) 1935) recommends the habitual eating of **bran with meals** as an especially useful treatment for *chronic constipation in elderly individuals*. In his experience the bran treatment gets rid of the inconvenience of eating unusually large quantities of wholemeal bread, vegetables (including some uncooked vegetables), fruits and nuts in the endeavor (not always successful) otherwise to overcome the constipation.

In discussing **dietary** aids in the control of constipation, P. W. Brown (Minnesota Med. 19:221 (Apr.) 1936) stresses the importance of individual advice. He believes that diet has been unduly emphasized, whereas not enough

stress has been placed on the importance of changes in occupation, nervous strain, and the whole complex whirl of living. W. A. Bastedo (Rev. Gastroenterol. 2:279 (Dec.) 1935) also discusses foods, as well as bulk-producing drugs, in the treatment of chronic constipation. He recommends the roughage foods in cases of constipation due solely to lack of residues, but admits that very often these alone are not sufficient and must be supplemented by a bulk-producing drug. The importance of **water** in the maintenance of proper bowel function is stressed. R. Hutchison (Brit. M. J. 1:374 (Feb. 22) 1936) doubts that dietetic treatment alone is likely to succeed in any except the slighter cases of atonic constipation. He believes that large and bulky residues may aggravate the trouble by placing too much of a load on an enfeebled bowel.

In view of the belief of A. F. Hurst (Lancet 1:1483 (June 29) 1935) that all cases of constipation are due to dyschezia, the admonition of F. E. Clow (New England J. Med. 213:1187 (Dec. 12) 1935) that "no case of constipation, in all honesty, should be treated without rectal examination," is not only obvious, but timely. The majority of cases of constipation, Hurst writes, can be cured by reestablishing the conditioned reflex upon which successful defecation depends. Simple explanation of the physiology of defecation and encouragement are often all that is required.

The value of selective **drugs** in the treatment of constipation is discussed by M. G. Mulinos (Rev. Gastroenterol. 2:292 (Dec.) 1935). He stresses the importance of knowing intimately the drugs which are used. A daily bowel movement is not necessary for a state of health and the routine use of laxatives to "open the bowels" is contrary to physiological good sense. Mulinos classifies

laxatives and purgatives and discusses the importance of **descending dosage** in effecting a cure of habitual constipation. This same theme is stressed by W. R. Houston ("THE ART OF TREATMENT," The Macmillan Company, N. Y., 1936), who writes that "what is needed is the mildest medicine in the smallest dose that will produce the desired results." Houston advises liquids or powders rather than pills, because small alterations in dosage cannot be made with the latter.

In an interesting contribution on motility disturbances of the intestine and their treatment, K. Gutzeit (München, med. Wchnschr. 82:1021 (June 28) 1935) discusses chronic gastroenteritis (colitis) with its alternating periods of "spastic" constipation and diarrhea. Further on he speaks of most cases of constipation as a mixture of spastic, atonic, dyskinetic and hyperkinetic types. He points out, for example that a large percentage of cases, previously considered habitual constipation, show accelerated passage through the small intestine. Knowing this, the type of treatment must not be a drastic purgative or an indigestible diet, since either of these will eventually aggravate the colon constipation and superimpose upon it a secondary colitis.

L. F. Rettger, M. N. Levy, L. Weinstein and J. E. Weiss ("LACTOBACILLUS ACIDOPHILUS AND ITS THERAPEUTIC APPLICATION," Yale University Press, New Haven, 1935) renew their interesting study on acidophilus milk and other acidophilus preparations. If used correctly, these preparations are especially beneficial in cases of simple constipation. Since other laxatives interfere with the effectiveness of the **acidophilus treatment**, they should be omitted. However, the importance of the oral administration of **dextrin** and **lactose**

in prolonging the activity of an acidophilus implantation is stressed. This form of therapy seems promising, especially if it is remembered that con-

tinual replenishment of the acidophilus strain by ingestion of acidophilus milk is necessary in the great majority of patients.

## VITAMINS AND VITAMIN DEFICIENCIES

By JOHN H. WILLARD, A.B., M.D.

### VITAMIN A DEFICIENCY.—

J. H. Musser (South. M. J. 28:834 (Sept.) 1935) states that it has been definitely shown in the past 3 years that this vitamin is present in certain yellow plants containing the provitamin A, carotene. Halibut-liver oil is the richest source of vitamins A and D. Milk is also an important source. In plants the chief sources are yellow-rooted and green-leafed vegetables. The richest plant source is the apricot.

While definite deficiency is rare, many writers have produced evidence that slight deficiency may result in decreased resistance of epithelial tissue to infection; and P. C. Jeans and Z. Zentmire (J. A. M. A. 102:892 (Mar. 24) 1934), who developed a test for vitamin A deficiency based on light sensitivity of the eye, have found mild forms of this deficiency to be very common in children in Iowa. This test is based on the premise that "night blindness" is an indication of vitamin A deficiency. The ability to adapt to night vision is measured by means of a regulated beam of light passed through a perforated disc and a wedge-shaped filter, the reading depending upon the number of perforations which are visible at various intervals after a sudden change from a brightly lighted room to a darkened room.

Jeans and Zentmire (*Ibid.* 106:996 (Mar. 21) 1936) "found that 26 per cent. of rural and 53 per cent. of a village group of Iowa children presented evidence of vitamin A deficiency; in an urban group the proportion for the

higher economic level was 56 per cent., for a middle level 63 per cent., and for a low economic level 79 per cent." All except 3 of the group of 78 who were treated with vitamin A developed normal dark adaptation.

I. O. Park (Am. J. Digest. Dis. and Nutrition 3:193 (May) 1936) states that in his experience the visual photometer method has proved an accurate method for the detection of vitamin A deficiency. In a series of several hundred persons the test showed considerable uniformity. A striking finding was that in over 100 supposedly normal individuals 83 per cent. showed evidence of deficiency. Many of these persons complained only of lassitude, nervousness, or a general lack of a sense of well-being. It was further found that all persons recently recovered from acute infections, such as pneumonia or bronchitis, showed vitamin A deficiency. From a clinical standpoint the following symptoms were noted: General lack of vigor; fatigue out of proportion to the difficulty of the task or the age of the individual; lack of luster of the cornea; nervous irritability and loss of sleep; dryness of the hair and roughening of the skin; ptosis of the eyelids; visual difficulties similar to those which are characteristic of night blindness.

L. K. Sweet and H. J. K'ang (Am. J. Dis. Child. 50:699 (Sept.) 1935) report studies on 203 patients suffering with various forms of vitamin A deficiency, including material from 17 autopsies and 22 biopsies. They found lesions

of the eye to be most common, with respiratory tract changes second in frequency. While the diet seemed to be the most important etiologic factor, abnormalities of absorption and utilization were frequently encountered.

**Urinary Lithiasis.**—Recent literature contains many references suggesting a relationship between vitamin A deficiency and urinary lithiasis. Two mechanisms have been suggested: (1) The calculi form because deficiency of vitamin A (in the rat) results in keratinization and desquamation of the lining epithelium of the urinary tract, a process that supplies the organic nidus for the deposit of crystalloids. (2) The calculi form because deficiency of vitamin A in the diet results in strong urinary alkalization, either as a primary effect or secondary to infection.

After a careful review of the evidence, the Council on Pharmacy and Chemistry of the A. M. A. (J. A. M. A. 105:1983 (Dec. 14) 1935) concluded that the existing evidence did "not warrant claims for the use of any of the vitamins, and particularly of vitamin A in the prevention and treatment of urinary lithiasis."

**Relation to Liver Function.**—Several references to the relation between liver function and utilization of vitamin A have appeared in the literature. E. P. Ralli, A. C. Pariente, H. Brandaleone and S. Davidson (*Ibid.* 106:1975 (June 6) 1936) studied the effect of carotene administration to 4 diabetic and 4 normal individuals. It was found that blood carotene levels rose higher in the *diabetics*. It is suggested that in diabetes the liver lacks the ability to convert carotene to vitamin A. Storage of unconverted carotene by the liver was thought to interfere with further absorption from the blood, resulting in carotenemia.

Although the association of *obstructive jaundice* and clinical manifestations of what is now recognized as vitamin A deficiency was described by writers in the last century, it was not until 1923-4 that a specific connection between hepatic disease with icterus and vitamin A deficiency, in spite of adequate diet, was described, according to M. D. Altschule (*Arch. Path.* 20:845 (Dec.) 1935). Since that time many cases have been reported. In all, the jaundice preceded the evidence of vitamin A deficiency.

The structural effects of vitamin A deficiency are characterized by atrophy of the epithelium of various organs and replacement with a stratified keratinizing epithelium. In infants the earliest appearance of keratinizing metaplasia is in the trachea and bronchi. The renal pelvis is next involved, then changes in the salivary glands, pancreas, uterus, thymus, esophagus, glands of nasopharynx, bladder, prostate, and seminal vesicles. Corneal changes appear late.

The author describes findings in 11 cases of congenital atresia of the bile ducts studied postmortem. Microscopic evidence of vitamin A deficiency was found in 6 instances, in spite of diets adequate in vitamin A.

Various explanations have been offered for this association of jaundice with vitamin A deficiency. It has been thought that the absence of bile prevents absorption of the fat soluble vitamin. This is supported by animal experimentation. Cure of the avitaminosis under these conditions can be accomplished by parenteral administration of vitamin A or by its administration with bile salts by mouth. The exact manner in which absorption is interfered with is not known, according to Altschule.

**Relation to Thyroid Function.**—H. Wendt (*München. med. Wchnschr.* 82:1160 (July 19) 1935) noted definite



benefit from vitamin A administration in cases of *exophthalmic goiter*. He found that serum carotene and vitamin A values were reduced in *hyperthyroidism* but returned to normal after successful therapy, either medical or surgical. In cases of *hypothyroidism* and *myxedema* the transformation of carotene to vitamin A seemed to be disturbed, according to this writer.

#### VITAMIN B DEFICIENCY.—

The clinical status of this vitamin or vitamin complex is still controversial. While a large amount of recent literature concerns itself with the relation of vitamin B<sub>2</sub> (G) to *anemias*, Musser points out that there is some contrary evidence. Castle and his associates have concluded that the "extrinsic factor" in primary Addisonian anemia is closely related to vitamin B<sub>2</sub>. However, this vitamin does not replace liver as an antianemic factor, and an active substance has been found which is free from vitamin B. (Brand, West and Stucky).

In regard to the relation of vitamin B<sub>2</sub> to *pellagra*, there is also some disagreement. Although the bulk of the evidence favors a close association between vitamin B deficiency and *pellagra*, Spies has reported improvement in *pellagra* patients on a vitamin deficient diet. There is experimental evidence that *glossitis* can result from vitamin B deficiency. Less controversy exists in regard to the importance of vitamin B<sub>1</sub> in *polyneuritis*. N. Jolliffe, C. N. Colbert and P. M. Joffe (Am. J. M. Sc. 191: 515 (Apr.) 1936) have shown the etiologic importance of vitamin B deficiency in *alcoholic neuritis*. They summarize the evidence as showing:

1. That the alcohol addict with *polyneuritis* has, as a rule, a qualitatively inadequate food and vitamin intake.
2. That assimilation or utilization of accessory food factors is often impaired by gastrointestinal or hepatic disorders.

3. That the clinical manifestations and the pathologic findings of "alcoholic" *polyneuritis* and *beriberi* are remarkably similar.

4. That ingestion of large amounts of whiskey, when accompanied by a vitamin-rich diet, supplemented by vitamins administered parenterally and per os, has no direct neurotoxic action.

The authors report a study of normal and *polyneuritic* patients using Cowgill's formula of the ratio between vitamin B intake, calories and body weight. They found that:

1. Every alcohol addict with *polyneuritis* had an estimated inadequate vitamin B intake.
2. No alcohol addict with an estimated adequate vitamin B intake had *polyneuritis*.
3. Every alcohol addict with estimated absolute deficiency of vitamin B for 21 days or more had *polyneuritis*.
4. *Polyneuritis* may develop in an alcohol addict as early as the seventh day of estimated absolute deficiency of vitamin B.

M. G. Vorhaus, R. R. Williams and R. E. Waterman (J. A. M. A. 105:1580 (Nov. 16) 1935) treated a group of 100 unselected cases of *poly- and localized-neuritis* with a preparation of **crystalline vitamin B<sub>1</sub>**. Only 8 per cent. failed to respond favorably; 44 per cent. became entirely symptom-free and 48 per cent. were definitely improved.

The same authors report the use of **crystalline vitamin B<sub>1</sub>** in *diabetes*. Improvement in glucose tolerance was noted in 54.6 per cent. of the cases. They state that there is evidence to show (in humans as well as animals) that carbohydrate intake bears a direct relationship to vitamin B<sub>1</sub> requirements, *i. e.*, the higher the carbohydrate intake, the quicker the depletion of B<sub>1</sub>.

J. B. Fitts (South. M. J. 28:920 (Oct.) 1935) has reemphasized the im-

portance of vitamin B<sub>1</sub> in *gastrointestinal function*. He studied a group of 75 patients having a diet deficient in vitamin B<sub>1</sub>. The most frequent diagnoses were gastric atony, ptosis, hypochlorhydria and achlorhydria, spastic colon with stasis, subnutrition, mild hypothyroidism. The effect of adequate vitamin B intake over a period of from 2 months to 2½ years was to improve well-being in all cases, with relief of flatulence, fullness and pressure in many. Constipation was definitely improved, and the gastric musculature showed less atony.

**Urinary Excretion Test.**—A method of removing vitamin B from urine by shaking with "acid clay" is described by L. J. Harris and P. C. Leong (*Lancet* 1: 886 (Apr. 18) 1936) as follows:

Using 24-hour specimens, the reaction is adjusted to about pH 5 (bromocresol green as an indicator) and 100 to 200 c.c. shaken with 1 Gm. Claret acid clay for 15 minutes in an automatic shaker. After filtering, the filtrate is again shaken with 1 Gm. of clay. The two specimens of activated clay are combined and added to the basal diet of a rat. The activated clay, if dried, will retain its full activity after 3 months storage in the refrigerator. The "bradycardia" method (Harris) of animal testing is used. Young rats (50 to 60 Gms.) are placed on a vitamin B deficient diet until the heart rate, as measured by electrocardiographic records, falls from 500 to 370 to 390. The unknown is then added to the diet in single graded doses using 4 to 5 rats. The heart rate is measured twice daily and the time taken for the heart to fall back to the original value at the beginning of the test is determined and compared with control animals receiving graded doses of international standard vitamin B<sub>1</sub>.

The average excretion in humans varies with intake and runs from 12-35 I.U. Relative deficiencies may be shown by response to test doses, a type of tolerance test, according to these workers.

**VITAMIN C DEFICIENCY.**—Recent identification of this vitamin and development of methods of synthesis and determination in urine, blood and tissues,

have resulted in prolific literature in this field. I. S. Wright (*Am. J. M. Sc.* 192: 719 (Nov.) 1936), who has written a very complete summary of the subject, included 182 references, and stated that in 1935 about 1,000 articles appeared and are at present appearing at the rate of about 50 per month.

According to Wright, hexuronic acid was isolated by Szent-Gyorgyi in 1928 and was identified as vitamin C in 1932. A complete description of the chemical and physical properties appears in an article by I. S. Wright and A. Lilienfeld (*Arch. Int. Med.* 57: 241 (Feb.) 1936).

**Requirements.**—It has been found that an adult of 70 kilograms of body weight requires about 50 mg. (¾ grain) of ascorbic acid per day. Citrous fruits and potatoes are the most common sources, but many vegetables and fruits contribute to the total. The C content of citrous fruits and tomatoes varies considerably. E. W. McHenry (*Canad. Pub. Health J.* 26: 124 (Mar.) 1935).

**Relation to Rheumatic Fever.**—J. F. Rinehart (*Ann. Int. Med.* 9: 586 (Nov.) 1935) reports that he and his associates have found that the defense mechanism of vitamin C deficient animals is less effective, and the ability to localize the infecting organisms is impaired in guinea-pigs. In these animals uncomplicated vitamin C deficiency produced definite atrophic and degenerative changes in the collagenous stroma of the heart valves. In scurvy with superimposed infection, striking lesions of a combined degenerative and proliferative character develop in the heart valves with considerable frequency. These lesions present many basic similarities to the early lesions of rheumatic fever. The heart muscle also showed some proliferative changes. Joint changes and subcutaneous nodules similar to those in rheumatic fever were also noted in vitamin C deficient guinea-pigs. The

fundamental tissue change in scorbutic animals has been described by many writers as a deficiency in intercellular cement substances. The effects of such change would be noted first in those tissues most subject to stress, hence the periarticular and valvular involvement.

This experimental work suggested to the authors the possible importance of vitamin C deficiency in association with infection in the etiology of rheumatic fever in humans. A study of the epidemiology of rheumatic fever strengthened this view, since it is known that malnutrition is frequently associated with this disease. It is very rare in the tropics where antiscorbutics are common in the diet. Rheumatic fever is more commonly seen in poorer people, is more common in cities, and has a familial tendency. The greatest seasonal incidence is in winter and early spring. While the importance of infection in rheumatic fever is undoubted, a specific organism has not been found. Upper respiratory infections are frequent, but the incidence of rheumatic fever relatively small. The author believes that the presence of latent scurvy may be the mechanism leading to susceptibility.

Little is known of the processes of assimilation and utilization of vitamin C, but it seems certain that there is very little storage in the body. Achlorhydria may increase the basal requirement, and infections and fatigue may deplete vitamin C stores.

A clinical study of children with rheumatic heart disease has definitely suggested the frequency of vitamin C deficiency and given evidence that adequate vitamin C intake is important to successful therapy, according to Rinehart.

Wright and his associates, however, have been unable to affect the course of rheumatic fever cycles by giving cevi-

tamic acid in doses as large as 1000 mg. (15 grains) or more daily.

**Utilization.**—Considerable vitamin C is believed to be lost in the urine and feces, the remainder being stored, utilized or resecreted in saliva, etc. The vitamin has been found in the adrenals, pituitary, ovary, tumors, blood serum, cerebrospinal fluid, sweat, aqueous humor and urine. In the author's experience, the average normal urinary excretion is 20 to 30 mg. ( $\frac{1}{3}$  to  $\frac{1}{2}$  grain) per day. With test doses (500 to 1000 mg.— $7\frac{1}{2}$  to 15 grains) the normal excretion rises to about 30 per cent. of the test dose, a return of 20 per cent. or less representing suboptimal storage. If 100 mg. ( $1\frac{1}{2}$  grains) or more are given gradually, excretion increases to 76 or more per cent., representing saturation.

In this connection, J. B. Youmans, M. B. Corlette, J. H. Akeroyd and H. Frank (Am. J. M. Sc. 191:319 (Mar.) 1936) studied daily excretion and degree of saturation in subjects whose diets were suspected of being deficient in various respects. For controls, a group of staff members was similarly studied. Two or more 24-hour determinations were made and averaged. Tests of saturation consisted of determining the per cent. of a test dose (usually 600 mg.) (10 grains) excreted in the urine in 24 hours. Fresh orange juice was used as the source of vitamin C, the ascorbic acid content being determined by titration.

It was concluded that the lowest normal excretion of ascorbic acid is 20 mg. ( $\frac{1}{3}$  grain) per day. After saturation, 80 to 100 per cent. of the test dose was excreted in the urine. Small doses given to unsaturated persons caused little or no effect on urinary excretion. Excretion of less than 20 per cent. of the test dose of 600 mg. (10 grains) was thought to indicate some degree of deficiency.

### *Sources of Error in Determination.*

Wright points out that other reducing substances may occur in urine, such as glutathione, cysteine and ergothioneine, which may alter results. They may be removed by precipitation with mercuric acetate. The urine must be titrated soon after voiding, even 10 per cent. glacial acetic acid not being a good preservative. The loss is decreased by storage in dark bottles or in the dark at refrigerator temperature. Addition of sulphuric acid to pH 3 is suggested.

**Blood Content.**—Although there is considerable disagreement as to the state of vitamin C in the blood, Wright believes the method of C. J. Farmer and A. F. Abt (Proc. Soc. Exper. Biol. and Med. 32:1625 (June) 1935; 34:146 (Mar.) 1936) for determining reduced cevitamic acid to be the most reliable at present.

**Capillary Fragility.**—Wright states that the relation of vitamin C to capillary resistance or fragility is a moot question. It is his feeling that blood determinations do not necessarily indicate the clinical status, and that capillary fragility may be a more reliable index of sub-clinical scurvy than blood levels. It is pointed out that other conditions may produce capillary fragility, such as thrombocytopenic purpura; poisons, such as neoarsphenamine; toxins, as in scarlet fever, and diphtheria, anemia, menstruation, etc.

The author suggests the use of pressure on the upper arm, using the blood-pressure cuff inflated to a pressure midway between the systolic and diastolic blood-pressures. Two areas 2.5 cm. in diameter on the forearm 4 cm. below the elbow are marked off and the number of petechiæ appearing after 15 minutes determined. Up to 10 are considered normal, and 10 to 20 as upper limits of normal.

According to D. Greene (J. A. M. A. 103:4 (July 7) 1934), capillary fragility in scurvy was first described by Hess, in 1914. Göthlin, in 1933, outlined a method of measuring capillary resistance by means of pressure applied with a blood-pressure cuff. The number of petechiæ appearing in a marked area 60 mm. in diameter at the bend of the elbow after a pressure of 50 mm. of mercury for 15 minutes, and the number after pressure of 35 mm. for 15 minutes is determined. If the higher pressure does not produce more than 4 petechiæ, the test is considered normal. If more than 8 appear with the higher pressure, and more than 1 with the lower pressure, vitamin C deficiency is believed to be present. Green found the test to be positive in many well nourished children whose diet was thought to be adequate, and concluded that a positive test did not necessarily indicate a state of vitamin C deficiency.

The relationship of plasma cevitamic acid to capillary resistance has been studied by A. F. Abt, C. J. Farmer and I. M. Epstein (J. Pediat. 8:1 (Jan.) 1936). A method was devised for measuring cevitamic acid in plasma by titration against sodium 2:6 dichlorobenzenoncindophenol. The normals in adults by this method were from 1.19 to 2.66 mg. per cent. In children, values less than 0.75 to 0.80 mg. per cent. indicated subnormal vitamin C intake. Using the Cutler-Johnson apparatus, the authors failed to find any close relationship between plasma values and capillary resistance.

It is of interest that cord blood in newborn infants gave figures almost identical with mothers' venous blood, suggesting that the infant supply is entirely obtained from the mother.

**Therapy.** Scurvy. Wright states that the first cure by means of **crystalline vitamine C** was reported by

Schultzer in 1933. Since then ample evidence of the curative value of this material has appeared. The author warns that "scurvy does not always begin in the classical way, but the symptoms complained of may be hemorrhages under the toe-nails, bleeding from the bowels, easy bruising, small scleral hemorrhages and the more common bleeding from the gums, commonly confused with pyorrhea. Weakness and secondary anemia are often present. These symptoms, with a marked increase in the capillary fragility, and a history of a vitamin C low diet, should suggest the diagnosis." "Blood and urine studies should be looked upon as confirmatory, with the above mentioned limitations. They may, however, be of utmost importance in determining the conditions of vitamin C unsaturation, a necessary precursor to scurvy."

**HEMORRHAGIC CONDITIONS.**—There are several reports in the literature of satisfactory treatment of *Schönlein-Henoch's purpura*, *hemophilia* and *thrombocytopenic purpura*. Wright has been unable to verify these results and calls attention to the difficulty of evaluating treatment in these conditions which are subject to spontaneous remissions. However, many patients with scurvy have low platelet counts and the condition might be mistaken for some other hemorrhagic disease.

**GASTROINTESTINAL ULCERS.**—Musser cites reports of *peptic ulcers* developing in scorbutic guinea-pigs. Wright states that there is no good evidence of any connection between vitamin C deficiency and peptic ulcer.

The latter believes that some cases of so-called *colitis* may result from vitamin C deficiency. There is evidence that **vitamin C** administration to some organic types of colitis has resulted in general improvement and a decreased tendency to bleeding. It is suggested

that in any gastrointestinal disorders requiring a low vitamin C containing diet, *preventive* doses of **cevitamic acid** should be added in doses of 50 to 100 mg. ( $\frac{3}{4}$  to  $1\frac{1}{2}$  grains) per day.

**TUBERCULOSIS.**—It has been shown that in any febrile condition the vitamin C requirement may be increased. In animals there is evidence that this vitamin is of assistance in the treatment of tuberculosis, and it has long been recognized that **vitamin C** in the diets of tuberculous patients seemed to be of help. Recent work suggests that it may be of particular value in *intestinal tuberculosis*.

**PNEUMONIA.**—While there is no evidence that the clinical course of pneumonia is altered by use of vitamin C, it has been shown that there is a definite decrease in urinary excretion in this disease, according to Wright.

**SKIN PIGMENTATION.**—While opinions still vary, there is evidence that vitamin C may be closely related to abnormal skin pigmentation. Reports have shown that the pigmentation of Addison's disease has been benefited by **cevitamic acid** administration. It is also suggested that pigmentation may result from vitamin C deficiency alone, although Wright believes the evidence is not conclusive.

**RELATION TO DIPHTHERIA TOXIN.**—C. W. Jungeblut and R. L. Zwemer (Proc. Soc. Exper. Biol. and Med. 32: 1229 (May) 1935) showed that diphtheria toxin was inactivated by vitamin C *in vitro* and that **cevitamic acid** seems to protect guinea-pigs against fatal diphtheria intoxication. This observation has been confirmed by C. G. King and M. L. Menten (J. Nutrition 10: 129 (Aug.) 1935).

**VITAMIN D DEFICIENCY.**—The evidence that vitamin D deficiency is closely related to *hyperparathyroidism* has been summarized by R. M. Wilder

and L. P. Howell (J. A. M. A. 106: 427 (Feb. 8) 1936). The theory has been offered that stimulation to hyperfunction of the parathyroids results from D deficiency in a way similar to stimulation of the thyroid by lack of iodine. This stimulation may result in adenomatous change in the gland. These authors have reviewed the records of 135 cases of hyperparathyroidism, particularly from the standpoint of geographical location, and have concluded that the greatest number of cases have been reported from areas where sunshine vitamin D exposure is likely to be limited either by atmospheric conditions or by modes of life.

The possibility of overdosage of vitamin D has been pointed out by recent writers. According to Musser, the suggested dosage of *viosterol* for prophylaxis is about 1500 units, while curative doses should be about 3000 units. Toxic effects may occur with 10,000 units daily, and cause nausea, vomiting, diarrhea, anorexia, weakness, lassitude, dizziness and incoördination.

#### VITAMIN E DEFICIENCY.—

Animal experiments have shown that deficiency of this vitamin may result in *sterility*, not only in the female but also in the male. Musser states that testicular changes may occur which do not regenerate on adequate supply of the vitamin.

#### VITAMIN F DEFICIENCY.—

Certain unsaturated fatty acids are apparently necessary to prevent *sterility* even in the presence of adequate vitamins A, E and D. H. M. Evans, S. Lepkovsky and E. A. Murphy (J. Biol. Chem. 106:431 (Sept.) 1934) include this deficiency under the heading of vitamin F.

**GASTROINTESTINAL FUNCTION AND DEFICIENCY.**—Much of the recent literature emphasizes the frequent association of gastrointestinal

disorders and deficiency syndromes. Recent evidence that deficiency may result from digestive disturbances has been reviewed by M. B. Strauss (J. A. M. A. 103: 1 (July 7) 1934).

Castle and his associates have shown that not only may *pernicious anemia* arise from the absence of an "intrinsic" gastric factor, but also from deficiency of an "extrinsic" or food factor apparently closely related to vitamin B<sub>2</sub> (G), the anti-pellagra vitamin. The *macrocytic anemias of the tropics*, certain *anemias of pregnancy*, and the *anemia of sprue* are believed to be of the latter type. *Primary* types of *anemia* have also been described in persons suffering from diarrheas of various types, apparently the result of lack of absorption of the necessary food factors.

*Pellagra*, probably due to lack of vitamin B<sub>2</sub> (G), in Northern States is usually seen in individuals showing gastrointestinal abnormalities or in alcohol addicts. Carcinoma of the stomach, pyloric obstruction, cancer of the ileum and colon and ulcerative colitis are a few of the many lesions described in cases of clinical pellagra.

*Peripheral polyneuritis* (beriberi), apparently due to deficiency of vitamin B<sub>1</sub>, is also frequently seen in association with digestive disturbances, as in alcoholics, pregnancy with pernicious vomiting, pyloric stenoses, celiac disease, dysentery, etc.

D. L. Wilbur (M. Clin. North America 19:463 (Sept.) 1935) states that deficiencies may depend on atrophy of mucous membrane, changes in secretion, absence of bile salts, loss of gastrointestinal secretions, and mechanical factors causing obstruction or incomplete absorption.

#### ENZYMES AND DEFICIENCY.

- B. Sure, M. C. Kik and K. S. Buchanan (Proc. Soc. Exper. Biol. and Med. 33: 78 (Oct.) 1935) have reported

a reduction in efficiency of digestion of pancreatic lipase but not in trypsin or erepsin in vitamin B deficiency. An increase in serum phosphatase was noted in this condition. In vitamin A deficiency there is a large decrease in concentration of blood serum esterase and an increase in hepatic lipase. The writers conclude that in vitamin B deficiency there is a marked decrease in the efficiency of fat digestion. No disturbance in the digestion of protein or starches was found in either vitamin A or B deficiency.

### MULTIPLE DEFICIENCIES.—

The frequent occurrence of multiple deficiencies has been stressed by many writers. R. L. Haden (J. A. M. A. 106: 261 (Jan. 25) 1936) points out that very frequently deficiencies cannot be definitely classified as pellagra, beriberi or scurvy, but are multiple and the symptoms of various deficiencies may be present in the same individual. The systems involved and the clinical conditions resulting from deficiencies are summarized in TABLE I and II which follow.

TABLE I.—*Systems Involved and Lesions Observed in Deficiency Disease in Adults*

| System                               | Lesions Observed as Manifestation of Deficiency   |
|--------------------------------------|---|
| I. Skin and other epithelial tissues | (1) Atrophy, (2) scaling, (3) dermatitis, (4) pigmentation, (5) ulceration, (6) cornification   |
| II. Nervous system . . . . .         | A. Neuritis: (1) pain, (2) paresthesia, (3) weakness, (4) paralysis<br>B. Degeneration of spinal cord: (1) lateral column, (2) posterior column<br>C. Cerebral: (1) mental disturbances<br>D. Disturbance of function: (1) tetany |
| III. Alimentary tract . . . . .      | (1) Anorexia, (2) stomatitis, (3) glossitis, (4) atrophy of tongue, (5) achlorhydria, (6) loss of specific ferments, (7) diarrhea, (8) loss of tone of gastro-intestinal tract, (9) ulceration of intestine                       |
| IV. Hematopoietic system . . . . .   | (1) Macrocytic anemia, (2) hypochromic anemia, (3) microcytic anemia  |
| V. Vascular system . . . . .         | (1) Hemorrhage, (2) easy bruising, (3) edema  |

TABLE II.—*Clinical Conditions Associated with Specific Nutritional Deficiency*

| Nutritional Factor                   | Clinical Signs of Deficiency  | Clinical Syndrome ("Disease")   |
|--------------------------------------|---|---|
| Calcium . . . . .                    | Increased nerve irritability  | Tetany  |
| Iron . . . . .                       | Anemia of hypochromic and often microcytic type                             | Hypochromic anemia  |
| Vitamin A . . . . .                  | Epithelial defects  | Ophthalmia, urinary calculi, night blindness                            |
| Vitamin B . . . . .                  | Anorexia, neuritis, edema   | Beriberi, multiple neuritis   |
| Vitamin B <sub>2</sub> (G) . . . . . | Glossitis, dermatitis, neuritis, mental disturbances                        | Pellagra (?)  |
| Vitamin C . . . . .                  | Hemorrhage due to vascular defects  | Scurvy  |
| Anti-pernicious anemia factor        | Glossitis, diarrhea, anemia of macrocytic type, degeneration of spinal cord | Pernicious anemia, subacute combined degeneration of spinal cord, sprue |

This type of multiple deficiency is illustrated by several cases, including multiple neuritis with hypochromic anemia; anemia and paralysis due to polyneuritis in pregnancy; macrocytic anemia with peripheral neuritis, sprue and tetany; pernicious anemia and sprue with low blood proteins; pellagra and pernicious anemia; pellagra, mild scurvy and hypochromic anemia; iron deficiency anemia with subacute combined sclerosis of the cord; pernicious anemia and iron deficiency anemia together.

Certain *symptoms and signs* are listed by the author as suggesting various deficiencies: *Macrocytosis of the red cells* suggests deficiency of the anti-pernicious anemia factor, and *hypochromia* suggests iron deficiency; *hyperirritability of the neuromuscular mechanisms* suggests lack of calcium; *glossitis or lingual atrophy*, as well as *peripheral nerve disturbances*, are suggestive of vitamin B<sub>2</sub> deficiency; *easy bruising* and unexplained *edema* should suggest vitamin C deficiency.

J. B. Youmans (South. M. J. 28: 843 (Sept.) 1935) states that in patients with deficient diets a common symptom is *edema* associated with low serum protein, but not always relieved by adequate protein intake. These patients recover much more rapidly if the condition is acute, which suggests that in chronic deficiency difficulties of absorption or utilization may appear. Another common symptom in these patients is *tenderness of the extremities* which does not respond to vitamin B, and *anorexia* which is not benefited by B administration. Likewise, symptoms suggestive of vitamin C are seen which do not respond satisfactorily to specific therapy.

Youmans believes these findings are indicative of interrelations of vitamins. *Edema* may be characteristic of one form of beriberi, yet it occurs in pellagra, in scurvy, and may occur under conditions of low protein intake apparently

uncomplicated by the presence of other deficiencies. *Subcutaneous hemorrhages* are typical of at least well-developed scurvy, yet they are found in pellagra, in beriberi, and in patients with nutritional edema. *Nervous system lesions* are considered pathognomonic of beriberi, yet they have been reported in scurvy, in vitamin A deficiency, and are frequent in pellagra. The *pain and tenderness* present in some cases of nutritional edema also occur in beriberi and scurvy. *Gastrointestinal disturbances* are common in both pellagra and beriberi, and *anemia* occurs in all forms of deficiency. "We are largely ignorant of the inter-relationship between various accessory food factors and the effects of their deficiencies of the requirements, absorption and utilization of one another."

**RELATION OF VITAMINS TO HORMONES.**—While there is little evidence at present to definitely link vitamins with hormones and enzymes, R. Karrer (J. A. M. A. 106: 1748 (May 16) 1936) believes that the lines of demarcation between these substances will become increasingly indistinct as knowledge increases.

**THERAPY.** The Council on Pharmacy and Chemistry of the A. M. A. (*Ibid.* 105: 1037 (Sept. 28) 1935) cautions against the use of polyvitamin preparations, not only on the grounds of unscientific therapy, but also because the interrelation of vitamins is not understood. There is some evidence that a definite antagonistic action may occur, as for instance some investigators have found that large amounts of vitamin A concentrate may be responsible for a disturbing effect on vitamin B. It has also been reported that vitamin A may interfere with the curative action of vitamin C. Thus, cases of scurvy have been reported in children taking adequate orange juice but in combination



with cod-liver oil. On the other hand, vitamin B is believed to lessen the toxicity of excessive doses of vitamin D. In the absence of more definite knowl-

edge of the interrelation of vitamins, the Council believes that mixed vitamin therapy is at present on an unsound basis.

## HEMATOLOGY

By WILLIAM DAMESHEK, M.D.

### BLOOD-FORMING ORGANS. — DIAGNOSTIC PROCEDURES.

—By means of a complicated apparatus supplying an artificial "lung, kidney, and circulation," E. E. Osgood and A. N. Muscovitz (J. A. M. A. 106: 1888 (May 30) 1936) reported the successful culture of human bone-marrow in sufficient quantity for any hematologic or chemical procedure. These investigators outlined 18 different problems which offered promise of solution by this method. Among them is one which has disturbed many people, *i. e.*, the development of a practical test for the identification and standardization of the antipernicious anemia principle. Other problems have to do with carrying on test-tube experiments relating to the various factors at fault in anemia, leukemia, agranulocytosis, etc. Whether or not the method and the ambitious program outlined for it will prove of value remains to be seen.

Many articles continue to be written regarding *biopsy of the sternal bone-marrow*. Most of them are concerned with simple puncture of the marrow space with an abbreviated lumbar puncture needle. R. H. Jaffé (*Ibid.* 107:124 (July 11) 1936) contributes a comprehensive review of the problem and cites the findings at biopsy in the various hematologic conditions. Jaffé concludes that the bone-marrow biopsy with a trephine as practised by Custer and Dameshek is the method of choice for research and systematic studies, since it permits (1) sectioning of the marrow

with preservation of the topographic relations of the cells and also the preparation of smears and imprints. The REVIEWER agrees entirely with this view. In addition, he feels that the accuracy of the simple puncture biopsies is open to much question. Despite their relative inaccuracy, their simplicity is of great advantage when multiple punctures are contemplated. Furthermore, if more and more physicians will become interested in the findings in the marrow, however obtained, the pathologic physiology of the various "blood dyscrasias" will become better appreciated.

B. K. Wiseman, C. A. Doan and L. A. Erf (*Ibid.* 106: 609 (Feb. 22) 1936) bring out the very interesting *reciprocal relationship between the bone-marrow on the one hand and the lymphoid tissue on the other*. By suitable animal experimentation and clinical observations, they demonstrate that with increased bone-marrow activity, the lymphoid response becomes diminished and *vice versa*. They postulate that there is a physiologic cellular equilibrium existing between lymphoid and myeloid tissue. Removal of a large amount of lymphoid tissue, as by splenectomy, will result in an increased activity of the marrow. [This idea, although attractive, may be far from actuality and will require further experimental proof.]

**Methods.**—ANTICOAGULANTS. — The subject of anticoagulants is becoming increasingly important because of the rapidly growing use of the hematocrit and the sedimentation rate. T. B.

Magath and M. Hurn (Am. J. Clin. Path. 5:548 (Nov.) 1935) analyze the various anticoagulants which have been used and conclude that heparin produces no swelling, crenation, or laking; that dry oxalate causes much shrinkage of erythrocytes, necessitating multiplication of the hematocrit value obtained by 1.127; that sodium oxalate in 1.1 per cent. solution is suitable and causes no significant swelling or shrinkage. V. G. Heller and H. Paul get around the shrinkage caused by sodium or potassium oxalate by using a mixture of sodium oxalate with ammonium oxalate. If a standard amount is used for say 5 c.c. of blood, neither shrinkage nor swelling takes place and no correction factor is necessary. M. M. Wintrobe and J. W. Landsberg conclude from their investigations that the above mixture of the two types of oxalate is as effective and accurate in their determinations as the extremely expensive heparin.

**SEDIMENTATION RATE.** In the above-mentioned article, Wintrobe and Landsberg carry out an exhaustive investigation of the sedimentation rate in which such factors as anticoagulant, bore, length, and inclination of the tube, temperature, concentration of the red blood cells are analyzed. These authors, like Rourke and Ernste working with heparin, found it was necessary to correct the sedimentation rate for the hematocrit reading, which can conveniently be done in the Wintrobe hematocrit tube. They state it is not essential to make readings every few minutes; by using a correction chart, the reading at the end of an hour may be taken.

E. M. Greisheimer, A. Hodapp and E. Goldsworthy (Am. J. M. Sc. 190:775 (Dec.) 1935) found that sodium citrate is a highly satisfactory anticoagulant (0.5 c.c. of a 3 per cent. solution for 4.5 c.c. of blood). They come to the rather startling conclusion that heparin,

often considered the standard anticoagulant, increases the sedimentation rate in all cases. The sedimentation rate is being more and more utilized in studying diseases of the heart and is assuming a measure of diagnostic and prognostic importance. P. Wood (Quart. J. Med. 5:1 (Jan.) 1936) investigated the matter in 164 cases of heart disease and found that increased rates were present in active rheumatic carditis, syphilitic aortitis, and myocardial infarction. Angina pectoris of effort was associated with a normal rate; congestive heart failure with a decreased rate. They point out the diagnostic and prognostic implications and also the limitations of the test.

It should be remembered that the sedimentation rate is a relatively "gross" nonspecific test reacting sometimes unpredictably to many conditions. It seems justifiable, therefore, except possibly in research investigation, to use (1) a relatively inexact measure, say at the end of an hour, than to go to the trouble of taking readings every few minutes; and (2) some such anticoagulant as ammonium potassium oxalate or sodium citrate.

**BLOOD CELLS.** Intelligent observations of changes in the numbers and characters of the blood cells will often prove to be of great benefit in the study of many *infectious diseases*. Particularly is this true in those conditions in which long standing infection is present. A very stimulating contribution along these lines is presented in a symposium on Progress in Tuberculosis in which are featured articles by C. A. Doan (Ohio State M. J. 31:921 (Dec.) 1935) and by B. K. Wiseman (*Ibid.* p. 925). Liberation of the active chemical materials which make up the tubercle bacillus affects the tissues and (*among other things*) is reflected in alterations of quantitative relationships

and qualitative characteristics of the blood cells. Sabin, with her studies on the differential picture produced by the various fractions of the tubercle bacillus, has been able to state categorically that a certain fraction as the carbohydrate will produce a neutrophilic response, etc. Based on these and other observations, Wiseman lists the following hematological changes and what their significance might be:

R. B. C.:

High.—Obstruction in oxygenation.

Low.—Secondary infection predominating.

Hemoglobin:

Low.—Measure of degree of toxemia.

Low.—Inadequacy of iron reserve.

Neutrophils:

Qualitative changes measure toxemia.

Quantitative changes measure caseation.

Monocytes:

Measure degree of proliferation of lesions.

Lymphocytes:

Qualitative changes measure resistance.

Quantitative changes measure healing.

Sedimentation Index:

Measure of toxemia.

The word "intelligent" at the beginning of this section is used advisedly. It presupposes a profound knowledge of the various factors which might cause changes in the blood picture; it signifies that knowledge of inaccuracies of methods, variations in counts, and variations in cellular relationships from moment to moment be well understood (Cf. E. M. Medlar: Arch. Int. Med. 57:367 (Feb.) 1936). In other words, it is not possible to draw sweeping conclusions from routinely-done differential counts. If the analyst is also the technician and in addition has a wide knowledge of the disease in question, his conclusions will be of great value. Mechanical systems for deriving from mathematical formulæ and simplified slide rules the outlook of a certain disease are much to be deplored.

D. Mainland, B. DuBilier and C. B. Stewart (Canad. M. A. J. 33:667

(Dec.) 1935) and D. Mainland, B. K. Coady and S. Joseph (Folia. haemat. 54:8, 1935) set out to study the accuracy of *differential blood counting* and by extremely time-consuming investigations arrived at the conclusion that a good deal of variation existed between successive counts of the same film and duplicate counts of two films taken simultaneously. This is undoubtedly true, but how much practical significance attaches to this observation is doubtful, since the blood itself is no exact composition of cells and since no exact inferences should be drawn from a differential count.

W. E. Garrey and W. R. Bryan (Physiol. Rev. 15:597 (Oct.) 1935) review their careful work on *variations in white cell counts* and give an excellent review of the literature. Garrey's work has been abundantly confirmed, particularly that relating to the basal leukocyte count. Garrey and Bryan take up such factors as daily variations, posture, random activity, exercise, training, adrenin, digestion, starvation, climate, pregnancy, emotional states, distribution phenomena, and cell life span. This is an excellent review and should repay careful reading.

A. H. Washburn (Am. J. Dis. Child. 50:413 (Aug.) 1935) continues his *standardization of the blood of healthy young infants*. These studies are, of course, extremely important in the appreciation of what constitutes abnormality and are too often disregarded. In normal children, Washburn brings out that the total leukocyte count may vary widely and be subject to great fluctuation, particularly in the lymphocytes. So striking is this fluctuation that it is often unwise to reach a conclusion from the study of one blood smear.

A "previously undescribed granule within the lymphocyte" is described by E. A. Gall (Am. J. M. Sc. 191:380 (Mar.) 1936). This is a motile, re-

fractile globule normally present in the cytoplasm of 34 per cent. of lymphocytes. Its significance is unknown.

H. S. Dunning and J. Furth (Am. J. Path. 11:895 (Nov.) 1935) conclude that *microglia of the brain* and *histiocytes* are morphologically and functionally identical and constitute a single cell type. Monocytes may transform into cells indistinguishable from microglia. This observation is of great significance as indicating the functional capacities of the microglia, since if they are truly monocytes, they are then part of the widespread and important reticulo-endothelial system.

That the *white cells* in the circulating blood continue to be the objects of such intense study would seem to be explained by the relatively recent interest in the *monocyte* as a third type of blood cell; by the increasing use of the careful differential count of the Arneith-Schilling types, and by the gradual diffusion of the knowledge that the white cells of the circulating blood may (in a very limited way, to be sure) be considered as representing the various blood-forming organs. Reactions of the bone-marrow, the lymphoid system, and the reticulo-endothelial system can to some extent be predicted from the examination of a blood smear.

T. H. Mendell, D. R. Meranze and T. Meranze (Am. J. M. Sc. 192:316 (Sept.) 1936) continue their studies on the cytoplasmic and nuclear changes in *neutrophils* occurring in severe *infectious states*. The REVIEWER has pointed out many times that in pyogenic infections certain changes occur in the cytoplasm of the polymorphonuclear cells which in general constitute an index of the severity of the infectious process. A slight degree of "toxic" change results in irregularity in staining and spacing of the cytoplasmic granules; a moderate degree results in more striking

manifestations of the same type; a marked degree results in vacuolization of the cytoplasm. Mendell, Meranze, and Meranze found that degenerative cytoplasmic changes occurred earlier than nuclear changes (band forms, nonfilamentous forms) and were more valuable for diagnostic and prognostic interpretation than the Schilling hemogram. (Of course, this depends upon the point of view, and to a great extent in the particular problem at hand; knowledge and careful attention to both types of phenomena are of greater value than study of a single factor. J. Fleming (Quart. J. Med. 5:105 (Jan.) 1936) brings out the fact that the extent and type of *leukocytosis* in *lobar pneumonia* depends to a large extent upon the type of organism present. Thus, with Type I infection, a leukocytosis of over 20,000 is characteristic, while with Type II infections, a leukocytosis of less than 20,000 is usually found. If the age of the patient, the duration of the illness, and the bacterial type of the pneumonic infection is known, the prognostic value of the leukocyte count may be considerable. [The author thus brings out again the above statement that "intelligent observation is a prerequisite; also that lobar pneumonia is not one disease but that each type infection of lobar pneumonia is a law unto itself.]

J. B. Carey and J. C. Litzenberg (Ann. Int. Med. 10:25 (July) 1936) studied the *leukocyte count in pregnancy* and found that leukocytosis was a common feature. M. Alieff and R. Reckers (Klin. Wchnschr. 15:1522, 1936) describe some further cases of *Pelger's syndrome*. In 1930, Pelger described 2 cases which presented a constant and marked "shift to the left" of the polymorphonuclear cells, with the presence in the blood of large numbers of immature granulocytes, usually of the "young" type. Other cases were soon

described and Huet in 1932 found 2 cases in one family. Alieff and Reekers, when they found a typical case, studied the family (which was a large one) and discovered 13 cases in 40 individuals studied from 3 generations. The cause of this hereditary disorder of the bone-marrow white cells is not known; like sickling of the red cells, it may be an abnormal growth phenomenon.

A. Myerson, J. Loman and W. Dame-shak (Am. J. M. Sc. 192:560 (Oct.) 1936), in studying pharmacological *effects of benzedrine* in human subjects, found that this drug when injected caused a marked increase of the erythrocyte and leukocyte counts in normal subjects, probably by a "squeezing" action which resulted from vasoconstriction of such organs as the spleen and marrow. S. Levy-Simpson and B. H. E. Cadness (J. Pharmacol. and Exper. Therap. 56:389 (Apr.) 1936) performed similar experiments in guinea-pigs with a closely related drug, ephedrine, and demonstrated (by splenectomy) that the spleen is not essential for the rise in red cells, leukocytes, and platelets, but that ephedrine probably causes extrusion of these cells into the circulation from storage and hematopoietic centers.

I. Olef (Arch. Int. Med. 57:1163 (June) 1936) performed *differential counts* of the *blood platelets*, which he divides into 4 groups, depending upon their size. The larger platelets, seen with both increased and diminished activity of the marrow, are less active functionally than the smaller types which probably have high agglutinating powers.

W. Kempner (J. Clin. Investigation 15:679 (Nov.) 1936) was enabled to study the metabolism of human erythroblasts in a case of *erythroblastic (Cooley's) anemia* and found that they showed very high oxidative and fermentative metabolism, approximately 200 times greater than that of the normal

nonnucleated human red blood cells. O. C. Hansen-Prüss (Am. J. Clin. Path. 6:423, 1936) studied the blood cells in fresh preparations with dark-field illumination and states that this is a very simple and reliable method deserving of further use; by it, the malarial parasite is unusually well seen. Another unusual method is that of *infra-red photography of the blood cells* which was practised by A. Hittmair (Folia. Haemat. 55:37, 1936), who states that it may be of value in the further study of the derivation and morphology of these cells.

**ANEMIA.**—As emphasized by the REVIEWER on many occasions, anemia is the expression of some bodily change which because of one or several factors has resulted in reduction of the hemoglobin concentration or in the number of circulating red cells. Anemia is never primary, and is always secondary to some cause or causes whether or not they are readily discernible. The emphasis is now placed upon the cell size rather than upon the primary or secondary character of the anemia. Knowledge of the cell size may be obtained (1) by simple inspection of the stained blood smear, (2) by actual measurement of the diameter of at least 100 red cells, and (3) by determination of the hematocrit: red cell relationship (mean corpuscular volume). Knowledge of the cell size immediately affords an idea not only regarding possible etiology, but of the therapeutic possibilities. If the red cells are small (microcytic), an iron deficiency state is present, and if hemorrhage, infection, malignancy, etc., can be ruled out, a chronic hypochromic anemia may be being dealt with, and iron should be of great value; with large cells, some form of liver deficiency is probably present and liver extract should be beneficial;

if, on the other hand, the red cells tend to be of normal size, a destructive process of the marrow should be suspected, amenable neither to liver nor iron therapy.

Again, it should always be remembered that anemia, although a striking manifestation, is merely one symptom of many bodily changes: thus, in an iron deficiency state the symptoms of glossitis, grey hair, flabby skin, and flattened finger nails are just as important manifestations as the anemia itself. These symptoms are not the manifestations of anemia; rather it should be stated that the anemia and the other symptoms are manifestations of a more general iron deficiency state.

#### IRON DEFICIENCY STATES

(Chronic Hypochromic Anemia.—

**Etiology.**—Most interesting has been the decline of chlorosis and the rise of chronic ("primary") hypochromic anemia. Chlorosis, apparently so common in the Victorian era, was a disease of the virgins; chronic hypochromic anemia is a disease of the menopause. Thus both conditions, characterized by a chronic iron deficiency state, are associated with the beginning and end of the menstrual cycle. Although chlorosis is rarely described, it is not entirely defunct, as A. J. Patek, Jr., and C. W. Heath (J. A. M. A. 106:1463 (Apr. 25) 1936) bring out. These observers described 4 cases and demonstrated in them various factors which were probably responsible for the state of chronic iron deficiency: a poor, capricious appetite; a hereditary factor in the presence of an anemic mother; hypo- or achlorhydria; and menorrhagia. They emphasize that adolescent girls require much more iron than the adult male, chiefly because of the great increase in growth which takes place together with the onset of regular loss of blood. When a girl is already at a disadvantage because of

poor heredity, a poor diet, or a poorly functioning gastrointestinal tract, the added demands for iron by the growing organism probably are just sufficient to bring about the full blown picture of what has been called *chlorosis*.

The problem of iron metabolism is being pursued vigorously in various clinics. G. H. Whipple and F. S. Robscheit-Robbins (Am. J. M. Sc. 191: 11 (Jan.) 1936), in their famous colony of anemic dogs, found that iron given **intravenously** to a normal anemic dog will be practically completely utilized and returned quantitatively as new formed hemoglobin. Iron given by mouth does not result in such proportional hemoglobin production. Even the optimal dosage of iron will result in only about 35 per cent. utilization of the iron given. These investigators could find no difference in action between the ferrous and ferric forms of iron.

C. W. Heath (M. Clin. North America 19:1685 (Mar.) 1936) again emphasizes the *importance of normal intestinal absorption* upon the prevention of the anemic state. With malabsorption, as in chronic diarrhea from whatever cause, iron deficiency states readily develop, even though the iron content of the food is entirely adequate.

L. A. Gray and M. M. Wintrobe (Am. J. Obst. and Gynec. 31:3 (Jan.) 1936) studied 40 cases of hypochromic microcytic anemia of obscure origin and found many gynecological abnormalities, including uterine myomata, endometrial hyperplasia, and unexplained menorrhagia. Multiple pregnancies were common. They concluded that the anemia in these cases was the result of faulty alimentary function, defective diet, and excessive demands for hemoglobin (as with menorrhagia). R. L. Haden (J. A. M. A. 106:261 (Jan. 25) 1936) brings out the important fact that many conditions are characterized

by *multiple* rather than single nutritional *deficiencies*, whether in iron, vitamin B complex, antipernicious anemia substance, etc. The deficiency may be due to a deficient intake of the specific food factors for normal needs; an insufficient supply for abnormal needs, as in pregnancy; a defect in absorption or a disturbance in utilization.

The view of Strauss and Castle that the temporary reduction of gastric acidity with resultant impairment of gastric digestion is an important causative factor in the development of the *anemia of pregnancy* is criticized by F. H. Bethell (J. A. M. A. 107:564 (Aug. 22) 1936), who concludes that this anemia is due either to (1) a preëxisting iron depletion or (2) an inadequate intake of protein of high biologic value during gestation.

**Symptoms.**—In the presence of a state of chronic iron deficiency the following symptoms and signs of varying degrees of severity will inevitably develop: greying of the hair, with a peculiar “lack-luster” appearance; a wrinkled, flabby skin; sores at the corners of the mouth “*La Perlèche*”; a reddened and later an atrophied tongue; atrophied buccal and other mucous membranes; dysphagia and, at times, esophageal webs; achlorhydria (?); flattened, brittle finger nails; and, finally, a marked diminution in the amount of circulating hemoglobin with a resultant lowering of the color index, and microcytosis and achromia of the red blood cells.

**Treatment.**—Treatment with almost any preparation of **inorganic iron**, provided it is given in sufficient dosage, will almost invariably result in prompt amelioration of symptoms with improvement of the physical signs and the blood picture. L. J. Wits (Lancet 1:1 (Jan. 4) 1936) contributes a fascinating and important article on the therapeutic ac-

tion of iron in which are discussed “the hematopoietic area of the alimentary tract,” the normal and abnormal iron requirement, the potentiation and antagonization of iron, and the dosage of different preparations of iron. Wits discusses the variability in the individual reaction to the same dose of an iron salt; an average effective dose is that which produces an average increase of over 1 per cent. of hemoglobin a day in a sufficiently large sample of patients with achlorhydria and anemia. Injection of iron is hazardous because the therapeutic dose is so close to the toxic dose. The therapeutic activity of preparations by mouth is directly proportional to their solubility and to the ease with which they yield free ions of ferrous iron. The **soluble ferrous salts** are the most effective; they are utilized in from 20 to 100 per cent. of the dosage given, depending upon the dose given. [The REVIEWER uses **ferrous sulphate** (“*exsiccated*”) in a dosage of 12 to 15 grains—0.77 to 1.0 Gm.—daily.]

With regard to “potentiation” of iron, A. J. Patek, Jr. (Arch. Int. Med. 57:73 (Jan.) 1936), describes the results of administering **iron** and **chlorophyll** products, separately and combined, and orally and parenterally to patients with chronic hypochromic anemia. By using the “double reticulocyte response” method, he found that an enhanced effect occurred with the use of preparations of chlorophyll. The study suggests that the body can use preformed pyrrol substances in the regeneration of hemoglobin and should encourage the liberal use of **greenstuffs** and **protein foods** in the diet.

**PERNICIOUS ANEMIA.**—**Etiology.**—Pernicious anemia may be considered as a symptom complex which is the end-result of a long-continued deficiency of “liver extract” within the body. This deficiency state may be brought

about in many ways: through an inadequate diet, an impaired gastric function, disordered intestinal absorption, through depletion of storage reservoirs in the liver, or from a combination of these factors. The end-results of "liver" deficiency are seen characteristically in the hair, the tongue, the gastric mucosa, the central nervous system, and the bone-marrow. The megaloblastic changes in the bone-marrow are sooner or later reflected in the peripheral blood, which shows anemia with large red cells, leukopenia, and reduction in blood-platelets. Because of the striking character of the blood picture, the disease has for many years been considered as primarily an "anemia," whereas the anemia which is present is only *one* of the many manifestations of liver deficiency which, in turn, is brought about by many diverse causes. The anemia of the disease called pernicious anemia is no more a "primary" condition than is the anemia of a case of "secondary" anemia. In the first instance, however, the red cells are large (because of the megaloblastic character of the liver deficient bone-marrow), whereas in the second instance the cells are small and hypochromic.

Although many etiological factors may be cited as contributing to the development of the symptom complex, the outstanding feature is usually the striking *abnormality in the gastric juice*, which Castle demonstrated was due to the *absence of an enzyme* ("intrinsic substance") active in the digestion of protein and vitamin B containing foods ("extrinsic substance"). Without this enzyme, these foods were insufficiently digested, the bone-marrow (and presumably other organs, such as the central nervous system) did not receive sufficient material for normal activity, with the resultant well-known changes.

S. M. Goldhamer (Am. J. M. Sc. 191:405 (Mar.) 1936) found that "in-

trinsic" substance was present in cases of pernicious anemia but in greatly reduced amounts, chiefly because the gastric juice was itself greatly reduced in quantity. The degree of reduction in intrinsic substance varied from patient to patient. This work is important because it explains the development of pernicious anemia in some patients following more or less prolonged dietary deficiency and, conversely, the good response to treatment in certain instances following a good diet or the feeding of large amounts of vitamin B complex.

E. A. Greenspon (J. A. M. A. 106: 266 (Jan. 25) 1936) decided to re-analyze Castle's fundamental experiments upon the basis of another explanation which had suggested itself to him. He found that gastric extract (ventriculin) was without effect in the presence of pepsin, but that *depepsinized ventriculin* was highly effective. He felt that the extrinsic factor (meat) of Castle's feeding experiments acted simply as an agent in the adsorption of pepsin, thus rendering this enzyme inactive and allowing intrinsic substance to act unimpeded. In other words, the "extrinsic intrinsic" interaction of Castle was subject to a different interpretation than that given by its author. Greenspon concluded that it is not necessary to postulate the presence of an extrinsic factor in pernicious anemia but that the disease is inherently a defect in intrinsic substance.

This work of Greenspon's, which caused a mild sensation when reported in the Journal of the American Medical Association [where it received extensive editorial comment], has been uniformly rejected by a number of different investigators. Thus C. C. Ungley (Lancet 1:1232 (May 30) 1936) found that completely *depepsinized gastric juice* and *pepsin-free extracts of pylorus mucosa* had little or no hematopoietic



effect when given orally unless interaction with a source of extrinsic factor (*e. g.*, autolyzed yeast) was allowed. He also found that the interaction of intrinsic and extrinsic factor did not require incubation outside the body, implying therefore that Greenspon's experiments might have been misinterpreted because that observer failed to allow completely for that contingency. F. M. Hanes, O. C. Hansen-Prüss and J. W. Edwards (*J. A. M. A.* 106:2058 (June 13) 1936) obtained completely negative results by feeding depepsinized gastric juice to 5 patients with pernicious anemia; they also suggested that Greenspon's results might have been due to the presence of "extrinsic factor" either in the stomach of the patient or in the gastric juice of the donor. W. B. Castle himself (*Ibid.* 107:1456 (Oct. 31) 1936) repeated all of Greenspon's experiments, analyzed his own previous results, and conducted some new experiments. All of this work tended to show that Greenspon had not adequately controlled the factor of food administration, and that an interaction between the intrinsic and extrinsic substances must have occurred within the body. Castle concedes, however, that pepsin does have some inhibitory effect, especially when gastric juice digestion mixtures are allowed to stand for some time. Other facts not brought out by Greenspon are that the gastric juice in pernicious anemia is completely devoid of pepsin; gastric juice alone has no effect; ventriculin or gastric mucosa are not suitable for experimentation, since they contain (as Castle has shown) not only intrinsic but extrinsic substance which by their interaction provide bone-marrow stimulating material.

W. Berger and H. Grill (*Folia haemat.* 54:398, 1936) state that pernicious anemia is brought about (in the present state of knowledge) by (1) occult

causes, accounting for most of the cases; (2) parasites; (3) infections, such as lues; (4) impairment of hormones, as in pregnancy and old age; (5) gastrointestinal changes. Chemical causes are exceedingly rare, and they proceed to describe a case which is said to be due to long-continued *carbon monoxide absorption* from a badly functioning stove. The relationships between the stove, the carbon monoxide poisoning, and the development of the disease are, it must be admitted, well worked out, although nothing definite is proven. They speculate that continued absorption of carbon monoxide into the blood stream resulted in changes in the gastric mucosa, with diminution in the production of both hydrochloric acid and the various enzymes.

The first almost-completely-convincing experiment demonstrating the pathogenesis of pernicious anemia is that of D. K. Miller and C. P. Rhoads. These investigators, by feeding dogs a "black-tongue"-producing diet, were able to produce some of the symptoms and signs of both pernicious anemia and sprue; the fully-blown picture of pernicious anemia did not, however, develop nor was there relief with parenteral liver extract. It was concluded that the dog "was not suitable for the production of a pathology identical with that of the human disease." When, however, swine were used as experimental animals and fed a modified Goldberger-Wheeler black-tongue-producing diet, a symptom complex was produced characterized by macrocytic anemia, lesions of the oral mucous membranes, gastric achlorhydria, diarrhea, and motor weakness of the extremities. Not only were these typical clinical manifestations of pernicious anemia present, but the bone-marrow was typically "megalo-blastic," the gastric juice showed no trace of Castle's enzyme, and the liver, when extracted and

injected, was completely devoid of activity. Furthermore, when potent liver extract was injected into these anemic swine, typical reticulocyte and erythrocyte responses took place. Thus, Miller and Rhoads have been able, by the use of an *inadequate diet*, to reproduce in an experimental animal the complete picture of pernicious anemia. The nature of the exact inadequacy in the diet must at present remain unsettled. It is apparently not vitamin B<sub>2</sub>. Whatever the missing food factor is, however, its first effect when lacking, is an inflammation of mucous membranes, leading, in turn, to atrophy and achlorhydria. Whether or not these experiments can be wholly applied to man is not yet clear.

Although the experiments of Miller and Rhoads again point to the rather definite possibility that pernicious anemia is somehow concerned with vitamin B deficiency, no exact proof of this has yet been advanced. One has the feeling that somehow vitamin B is concerned, but experimentation, at least with animals, has thus far been unsatisfactory. It is a curious commentary that, in work with pernicious anemia at least, the swine is closest to the human in its reactions. M. C. L. Gildea, W. B. Castle, E. F. Gildea and S. Cobb (Am. J. Path. 11:669 (July) 1935), who had maintained for years the relationship between vitamin B and pernicious anemia and combined system disease, conducted some interesting experiments on dogs. They were able to produce disturbances somewhat similar to those of combined system disease by a vitamin B<sub>1</sub> deficient diet in dogs which were kept from dying by the temporary use of small amounts of vitamin B concentrate.

A most important article relating to the pathogenesis of pernicious anemia is that on the "Etiology and Treatment of Sprue" by W. B. Castle, C. P. Rhoads,

H. A. Lawson and G. C. Payne (Arch. Int. Med. 56:627 (Oct.) 1935). This paper is a model of clinical and experimental investigation and will doubtlessly be referred to hereafter as a classic on the subject. Sprue and pernicious anemia, these investigators demonstrate, are substantially identical diseases. Minor differences occur, to be sure, but these are no greater than among individual cases. Both diseases are examples of closely related *deficiency disease*, the chief manifestations consisting in disturbances of the tongue, stomach and intestines, the anemia, and (rarely in sprue) the degenerative lesions of the spinal cord. All the hematological, gastric, and bone marrow findings closely corresponded in the two diseases and the clinical manifestations were invariably benefited by adequate doses of parenterally injected liver extract. The inadequate dietary seemed more important in sprue than in pernicious anemia.

M. M. Wintrobe and H. B. Shumacker, Jr., (J. Clin. Investigation 14: 837 (Nov. 1935) contribute an intriguing paper on the relationship of *fetal hematopoiesis* to the macrocytic anemia of pregnancy and anemia in infants. These authors studied the blood of 12 obviously nonviable human fetuses removed by hysterectomy, together with that of rabbits, rats, pigs, dogs and cats fetuses. "Anemia" was always present in the fetus, gradually diminishing in severity as the fetus matured. The anemia was of the macrocytic variety, with extremely high mean corpuscular volumes and mean red cell diameters. The rising values in the red blood count with increasing maturity of the fetus was strikingly similar to the rising erythrocyte level with specific therapy in pernicious anemia. These observations bring up many interesting speculations: that the fetus suffers from a "liver deficient" state which gradually

becomes ameliorated as "liver substance" is removed from the mother; that in certain instances, the mother's store of liver substance may become so depleted that she herself will develop pernicious anemia; and that the very grave anemia of the newborn known as *erythroblastosis fœtalis* may be due to "liver deficiency." [The latter observation is to be questioned.] J. F. Wilkinson and M. C. G. Israels (Brit. M. J. 1:139 (Jan. 26) 1935) conceive that in certain cases of apparent pernicious anemia which do not respond to liver extract there may be an actual *inability to utilize liver* (*achrestia*—achrestic anemia). This is an attractive hypothesis which may be of service (at present) in explaining the refractoriness to therapy of certain cases of pernicious anemia.

A great to-do has recently been stirred up by the insistence of various authors in the identity of the macrocytic anemia associated with certain cases of hepatic disease with pernicious anemia (S. M. Goldhamer, R. Isaacs and C. C. Sturgis: Am. J. M. Sci. 188:193 (Aug.) 1934); and M. M. Wintrobe: (Arch. Int. Med. 57:289 (Feb.) 1936). The comments of Minot and Castle in the 1933 Year Book of General Medicine regarding this interesting subject should be read by those interested. They make this cogent observation: "Since macrocytosis is common to the anemias of leukemia, Hodgkin's disease, aplastic anemia, benzol poisoning, and other anemias seemingly unrelated to pernicious anemia, it is scarcely to be expected that deficiency of liver extract will be found in all instances of pernicious anemia. The clinical evidence and the logic are equally in favor of the macrocytic anemia of such patients as having no dependence on deficiency of liver extract."

**Treatment.**—Aside from etiological considerations, most of the articles about pernicious anemia are concerned with

therapy. A completely satisfactory method for the assay of various antianemic substances has not yet been discovered, despite some interesting observations regarding the reticulocyte responses which occur in guinea-pigs. B. M. Jacobson (J. Clin. Investigation 14:665 (Sept.) 1935) announced what was apparently the long-sought for solution for an *animal assay method for liver extract*. This involved the use of guinea-pigs which were "reactive" in the sense of a reticulocyte rise occurring after the administration intraperitoneally of a preparation of liver extract. In these reactive animals, a reticulocyte count of 2 per cent. or over occurring for 2 days within 6 days after the administration of a test material indicated a positive response; a negative response was present with a reticulocyte count of 1.8 per cent. or under in the same period. Not only did this investigator maintain that the reticulocyte response in guinea-pigs was a specific one (dependent upon a "liver deficient state in normal guinea-pigs"), but he went further and defined a unit of hematopoietic activity ("guinea-pig unit") with which he was able to assay quantitatively various substances including the "intrinsic" and "extrinsic" factors of Castle. Jacobson's work was soon confirmed by D. K. Miller and C. P. Rhoads (New England J. Med. 213:99 (July 18) 1935), who stated that "it must be shown clearly that the induction of the reticulocyte response depends upon the same pathological mechanism as that which obtains in the human being with pernicious anemia." Miller and Rhoads concluded that their experiments satisfactorily demonstrated this relationship. It is well, however, to await the test of time before accepting this method as proved. In a more recent article by L. S. Goodman, A. J. Geiger and T. G. Klumpp (J. Clin. Investigation 15:435 (July) 1936) there is this footnote from

a personal communication by Miller and Rhoads: "Further experimentation has advanced incontrovertible evidence that guinea-pig reticulocytes may increase to a level of over 2 per cent. from a variety of causes unassociated with the administration of substances effective in the treatment of pernicious anemia. Experiments are under way in an attempt to elucidate the cause of spontaneous variations in numbers of reticulocytes; such spontaneous variations demand that the greatest care be used in employing the guinea-pig as a test for antianemic substance." The article referred to of Goodman, Geiger and Klumpp would seem on its face to dispose effectively of Jacobson's method. A large and well-arranged series of experiments is presented which inevitably lead to the following conclusion: "The normal adult guinea-pig shows considerable and unpredictable spontaneous fluctuations in reticulocyte levels. These variations are of such a nature as to render this normal animal unsuitable for assaying the potency of materials effective in pernicious anemia."

The *human assay* of liver extract remains the only completely satisfactory one and this is beset with many difficulties which are discussed by W. Dameshek and W. B. Castle. These authors criticized the then current methods of labelling liver extracts and concluded that in the refinement of the various extracts potent material is lost to greater or less extent. [The Council of Pharmacy and Chemistry of the American Medical Association has taken cognizance of this and other work and has established (J. A. M. A. 105:1269 (Oct. 19) 1935) new requirements for the acceptance of liver and stomach preparations.]

M. Gänsslen (Med. Klin. 32:533 (Apr. 17) 1936) reports on the treatment of pernicious anemia with minimal

doses of a parenteral liver extract called "campolon." This investigator, who prepared the first commercial extract for injection, found that he could obtain strikingly effective results, often maximal, following the injection of only 2 to 6 c.c. ( $1\frac{1}{2}$  to  $1\frac{1}{2}$  dram) of extract (derived from 20 to 60 Gm.  $\pm 2\frac{2}{3}$  to 2 ounces) of liver, and given in 1 dose. In 1 case 2 c.c. ( $1\frac{1}{2}$  dram) of this relatively dilute extract *given once* resulted in an excellent reticulocyte response which was followed without further treatment by a rise in erythrocyte count from 1.8 to 4.1 million in 4 weeks. He makes the important observation that the daily injection of parenteral extract with the subsequent careful follow-up of the reticulocyte count [as recommended by Dameshek and Castle and prescribed now by the Council on Pharmacy and Chemistry of the American Medical Association] may be misleading, since the reticulocyte reaction obtained might all have been due to the first injection given. [This is true if maximal injections are given, but not when sub-optimal doses are administered.] Be this as it may, all observers are agreed that the maintenance dose varies greatly from patient to patient and must be determined in each case by careful follow-up study.

Efforts to isolate the *antianemic principle in liver* continue apace. H. Strandell (Nord. med. tidskr. 10:1217 (Aug. 3) 1935) by an as yet secret method has been able to derive from 100 grams of liver from 1 to 27 milligrams of material which is therapeutically effective. H. D. Dakin and R. West have isolated a product from liver extract effective in very small dosage and which contains at least 6 amino acids. Y. Subbarow, B. M. Jacobson and C. H. Fiske isolated from liver extract 2 substances both effective in guinea-pigs. Fraction "A," which was apparently 1-tyrosine, contained 16,700,-

000 guinea-pig units per gram of material. Fraction "C," which assayed 10,-660,000 guinea-pig-units, was apparently a complex purine such as is found in the wings of certain yellow butterflies. It should be noted that the work of Dakin and West and of Subbarow, Jacobson and Fiske seems to be mutually contradictory. The potency of the Dakin and West material has recently been investigated abroad by C. C. Ungley, L. S. P. Davidson and E. J. Wayne (Lancet 1:349 (Feb. 15) 1936) and found to be quite high in dosage of 100 to 600 mg. ( $1\frac{1}{2}$  to 10 grains). Subbarow, Jacobson, and Fiske's assays on human subjects have not yet been published.

Aside from these rather theoretical observations, the search for the most effective and the most conveniently used antipernicious anemia substance continues unabated. The development of liver therapy has been traced by G. R. Minot (Lancet 1:361 (Feb. 16) 1935) in his Nobel Prize lecture. It is an interesting commentary that when an injectable substance such as insulin is introduced, the medical public clamors for an oral preparation and then when an oral preparation such as liver extract is discovered, their cry is for an injectable material. Now there is available dry powdered liver extract, dry gastric extract, dry liver extract activated by gastric extract ("extralin"), liquid oral liver extract (both alcoholic and non-alcoholic), and a large number of assorted types of injectable liver extract. It is no wonder that the practitioner is sometimes bewildered by the wealth of material at his command and by the conflicting claims of rival manufacturers. It may be stated here that some few patients, chiefly those without neurological involvement, may be well maintained on one of the oral extracts, whether dry or liquid. Others, and especially those in whom neurological

symptoms are prominent, require frequent injections of a potent parenteral extract. This is given daily, twice weekly, weekly or biweekly, depending upon the type and severity of the case at hand. The REVIEWER is accustomed to use a so-called "concentrated" extract given usually weekly or biweekly and frequently supplemented either by liver itself or by some form of oral liver extract. One should not be misled at the present writing by the attractive promises of potency inherent in extreme concentration. Several observations have recently been made indicating that prolonged and intensive therapy with parenteral therapy is effective in the treatment of the neurological lesions of pernicious anemia (R. F. Farquharson; Canad. M. A. J. 33:473 (Nov.) 1935; M. B. Strauss, P. Solomon, A. J. Schneider and A. J. Patek, Jr.; J. A. M. A. 104:1587 (May 4) 1935).

Liver therapy is of value not only in pernicious anemia proper, but in all conditions in which "liver deficiency" is present, even when the cause (such as pregnancy, fish tapeworm, poor dietary) is readily apparent. Thus, W. B. Castle, C. P. Rhoads, H. A. Lawson and G. C. Payne (Arch. Int. Med. 56:627 (Oct.) 1935) report the remarkable effects in sprue.

Recently, a peculiar, shall we say, atavism, came into being, namely the idea that pernicious anemia is a "toxic" state, to be treated by a detoxifying agent, *i. e.*, **congo red**. This idea was promulgated by M. Massa and G. Zolezzi (Klin. Wchnschr. 14:235 (Feb. 16) 1935), who described the results of the injection of a 1 per cent. solution of congo red intravenously in 14 cases. Careful review of their cases will show that the favorable results are usually greatly delayed in their inception and frequently helped along by liver or other antianemic substances. More recently,

their work is said to have been confirmed by C. Mermod and W. Dock (Science 82:155 (Aug. 16) 1935), who treated 2 cases in similar fashion. They were also able to obtain rises in guinea-pig reticulocytes with the dye. What, if any, rationale there is to the procedure is as yet a mystery. Two cases observed by the REVIEWERS relapsed to very low levels when given congo red. It is no great prophecy to foretell that this new treatment is doomed to an early demise.

The therapeutic effects of **vitamin B** in pernicious anemia continue to be studied. D. K. Miller and C. P. Rhoads first fed mixtures of gastric juice incubated with vitamin B<sub>1</sub>-containing substances to patients with pernicious anemia and failed to obtain responses. However, when egg white (containing vitamin B<sub>2</sub>) and gastric juice mixtures were fed to the same patients, sharp increases in reticulocytes took place. Despite this striking experimental evidence, Miller and Rhoads are unwilling to conclude that vitamin B<sub>2</sub> and the anti-pernicious anemia factor are identical. This must await isolation of the vitamin in pure form. C. C. Ungley and G. V. James did some interesting experiments with various vitamin B concentrates and yeast autolysates in human pernicious anemia and at times, especially when "mannite" was used, obtained fairly satisfactory therapeutic results. This was especially true in those cases distinguished by a deficient dietary. H. C. A. Lassen and H. K. Lassen in their experiments with various fractions of vitamin B showed pretty conclusively that neither vitamin B<sub>1</sub> or vitamin B<sub>2</sub> had any antianemic effect in cases of pernicious anemia and that these substances were therefore not the "extrinsic" substance. Is it not possible that various investigators are working with different cases of pernicious anemia? Not every case of macrocytic anemia is brought about

in the same way. Some cases undoubtedly react to a good diet or to a high vitamin B diet; perhaps these have had a deficient diet. Those cases which do not, might have developed the pernicious anemia "complex" through some other mechanism.

**MACROCYTIC ANEMIA NOT PERNICIOUS ANEMIA.**—*Diagnosis.* An increase in the average red cell diameter and in the mean corpuscular volume is not pathognomonic of pernicious anemia. Aside from related conditions (due to dietary, gross gastrointestinal disturbance) which are in reality as much entitled to the designation "pernicious anemia" as the so called primary disease itself, there are a number of conditions associated with macrocytosis of the red cells. Much interest has developed in recent years in the macrocytic anemia of hepatic disease and its possible relationship to pernicious anemia.

M. M. Wintrobe (Arch. Int. Med. 57:289 (Feb.) 1936) has been one of the chief advocates of the essential identity of macrocytic anemia of disease of the liver with pernicious anemia. He studied 132 cases of severe hepatic disease, including examples of cirrhosis, malignant disorders, and various miscellaneous disorders. No anemia was present in 30 cases; macrocytic anemia in 43 cases; normocytic anemia in 40 cases; microcytic anemia in 19 cases. The mean red cell count in the group of cases with macrocytic anemia was 3.48 millions and the mean corpuscular volume 103 cu. micra. In 4 cases of macrocytic anemia there was some response to treatment with liver extract. Foci of extramedullary hematopoiesis were found in the spleens of several cases at postmortem examination. Wintrobe concluded that the macrocytic anemia of hepatic disease was morphologically similar to pernicious anemia,

if not identical with it. The evidence at present, Wintrobe states, suggests that when damage to the liver is so extensive that storage is interfered with and when it has been of sufficient duration to permit exhaustion of the hematopoietic principle already present, macrocytic anemia develops. Only a few studies of the bone-marrow were made in these cases, and these failed to reveal anything but slight hyperplasia in some of the cases.

There can be no question that the anemia in these cases of hepatic disease was due at least in part to disease of the liver, but very little evidence is presented which shows convincingly that the anemia is identical with that of pernicious anemia. Too much emphasis is placed, it seems to the REVIEWER, on minor changes in the mean corpuscular volume. Anything above 94 cu. micra is considered macrocytic; this may be strictly true, but many a case presenting anemia shows a mean corpuscular volume up to 105 cu. micra without definite macrocytosis being present as seen from the blood smear. The macrocytic anemia, if present, in certain of these cases might have been due to abnormalities of the red cells which have nothing in common with the fundamental megaloblastic abnormality of true pernicious anemia. The liver is undoubtedly a storage reservoir, but it is probably not the only one in the body; with loss of hepatic function, the body may still get "liver substance" through the diet and may call upon stores in the kidneys and other organs.

From the experimental side, G. M. Higgins and J. Stasney (*Folia haemat.* 54:129, 1936) produced cirrhosis of the liver in rats by causing them to inhale the *fumes of carbon tetrachloride*. A marked anemia of the macrocytic variety developed, although hypochromasia was (paradoxically enough) also present.

These authors felt that there was definite correlation between the extent of the hepatic cirrhosis, the degree of the anemia, and the extent of the macrocytosis. S. M. Goldhamer cites some previous experimental work in which an extract prepared from a case of severe alcoholic cirrhosis of the liver with a very low red cell count failed to produce a response in a case of pernicious anemia when it was given parenterally. Goldhamer states that 5 factors may produce a macrocytic anemia: (1) deficiency of extrinsic factor; (2) deficiency of intrinsic factor; (3) deficient absorption from the bowel; (4) deficient storage in the liver, and (5) lack of utilization by the body tissues. At the present state of knowledge, it is not possible to accept definitely the concept of Wintrobe and others that the macrocytic anemia of hepatic disease is identical with that of pernicious anemia. What has come out of these studies is the emphasis on the rôle of the liver as a storage reservoir and the fact that large red cells may occur with hepatic disease.

The fifth of Goldhamer's above 5 factors, namely that of impaired utilization, has recently been the subject of an interesting article by M. C. G. Israëls and J. F. Wilkinson (*Quart. J. Med.* 5:69 (Jan.) 1936). These authors describe a group of 4 cases in which, although the blood picture and most of the clinical features were quite typical of pernicious anemia, there was free  $\text{HC}_1$  in the gastric juice and failure of response to specific anti-anemic therapy. Despite numerous transfusions, the cases all ended fatally. Because the bone-marrow looked typically megaloblastic; because there was no response to liver therapy; because the liver itself when assayed later showed adequate anti-anemic substance—the authors concluded that there must be a failure of

utilization ("achrestia") of liver substance from the normal stores in the body and from substances injected into the body. They consider that although these cases are rare, they comprise a distinct group which are labelled "achrestic" anemia. Whether or not the speculation that there is impaired utilization is correct, the hypothesis is an intriguing one. Confirmation is needed before it can be accepted.

#### HEMOLYTIC ANEMIAS.—

**Types.**—It is customary to group under this title not only congenital and acquired hemolytic jaundice, but erythroblastic (Cooley's) anemia, and sickle-cell anemia, although it is recognized that the hemolytic factor in the latter two conditions may be slight.

As pointed out in other reviews, the greatest advance recently made in *congenital hemolytic anemia* is the recognition that the most important feature of the disorder is an abnormality of the red cells which are smaller and more spherical than normal and thus more ready to burst (Haden). This is brought out *in vitro* by the fragility test, in which the red cells come in contact with hypotonic solutions of salt. The spherical character of the cells is brought out not only by direct study, but by comparison of the percentage volume of packed red cells with the red cell diameter. The cell diameter in these cases is diminished, often greatly so, and yet the hematocrit may be normal or even increased. This can only be due to an increased thickness of the red cell which is a fundamental abnormality. This indicates very strongly that the fundamental defect in the disease is the production by the marrow of pathological red cells which, because of their abnormal spherical nature, are readily destroyed. There is, however, something to be said for the opposing view which has it that the abnormality lies

in an unusually active reticulo-endothelial system (spleen, etc.) which destroys more red cells than normally. Along these lines are the observations of G. M. Levi and A. Bairati (Am. J. M. Sc. 190:610 (Nov.) 1935), who demonstrated that following splenectomy in one case of congenital hemolytic jaundice, the red cells became larger and their fragility became somewhat diminished. This would indicate that the bone-marrow was capable of normal erythrocyte production, but that the spleen was primarily at fault. If the reader is particularly interested in this phase of the problem, two Italian articles are of great interest, that by G. Momigliano Levi (Hæmatologica 16:1001, 1935) and G. Dominici (*Ibid.* 17:185, 1936). The latter article gives a thorough discussion of the two types of theories involved, either or both of which may be correct.

Other associated abnormalities were studied by K. Hansen and E. Klein in a large family with the disorder: tower skull, broad root of the nose, numerous abnormalities of the eyes, bilateral mongolian fold, carious dental abnormalities, etc. In a discussion of the nature of congenital hemolytic disease, which he calls "*spherocytic disease*," Lehn-dorff states that this congenital disease may remain latent for a long time, but its manifestation may be brought on by such factors as infection, exposure, or overexertion. When fully developed, 3 characteristic symptoms are present: icterus, pallor, and splenomegaly; and 3 hematologic signs: microcytosis, increased fragility of the red cells, and increase of reticulocytes. Microcytosis is most striking, and the red cells are spherical and, therefore, have a greater volume than the normal erythrocytes. These spherical red cells being more fragile than normal, tend to be broken down more readily by the reticuloendo-



thelial system and, therefore, the spleen enlarges. Lehdorff feels that the nature of the disease is best explained by assuming a congenital abnormality of the erythropoietic system with the production of spherical rather than disc-shaped red cells. He feels that the treatment should be consistently palliative (**liver, iron, transfusion**) unless hemolytic crises supervene, when **splenectomy** is indicated.

A most unusual report is that of A. M. Scott (*Lancet* 2:872 (Oct. 19) 1935) who describes the sudden development of acute hemoclastic crises in 4 children of *one family*. Although the crisis of sudden anemia with jaundice occurred in sequence within a period of 3 weeks, no common cause could be demonstrated. All of the children showed unusually labile (accordion-like) splenic enlargement. The development of hemoclastic crises in cases of congenital hemolytic icterus, although rare, is an important phenomenon from the therapeutic standpoint, for unless energetic treatment, particularly **transfusions**, is resorted to, the patient may die of anemia. Certain of these cases may require "emergency" **splenectomies** as pointed out by Doan, Curtis, and Wiseman; C. A. Doan, B. K. Wiseman, and L. A. Erf; and C. A. Doan, G. M. Curtis and B. K. Wiseman (*J. A. M. A.* 105:1567 (Nov. 16) 1935) point out the striking results which occur with **splenectomy** in these cases. It is in this disease that the operation of splenectomy is most strikingly successful and productive of a permanent cure. The Ohio State group has done emergency splenectomies in individuals with hemoclastic crisis, and this has often resulted in a sudden spectacular release of red cells following ligation of the splenic pedicle while the patient is still on the operating table. Doan and his associates make much of a hypothetical "hemolytopoietic

equilibrium" which exists between the blood-forming and blood-destroying organs, and are inclined to underestimate the importance of the abnormality of the red cells as shown by others.

An occasional article is written of an unusual type of hemolytic anemia, apparently infectious in origin, and first described by Lederer in 1925 and Brill in 1926. The disorder is well described in case reports by F. Corelli (*Hæmatologica* 16:13, 1935) and H. Joules and L. M. Masterman (*Brit. M. J.* 2:150 (July 27) 1935). It is characterized by acute onset with high fever, dyspnea, extreme asthenia, icterus, macrocytic anemia, leukocytosis, marked increase in reticulocytes, some increase in normoblasts, and favorable prognosis with **transfusions** and **liver extract**.

**ERYTHROBLASTIC (COOLEY'S) ANEMIA.**—There has been no definite advance in the delineation of this disease which, like congenital hemolytic icterus, is characterized by excessive blood destruction in association with increased blood formation. The latter is frequently so striking that the enlarged marrow spaces result in defects (*striæ*) of the skull visible by x-rays. There is at least one important difference, however: splenectomy is of no value in Cooley's anemia. D. H. Kelly and L. F. Hill summarize the findings in this disease: constant racial (Mediterranean peoples) and familial incidence, mongoloid facies, many nucleated red cells in the peripheral blood, splenomegaly, changes in the bones. H. W. Josephs groups erythroblastic anemia, sickle-cell anemia, and congenital hemolytic anemia together, since they not only have definitely constitutional factors, but all have somewhat similar blood pictures, dependent upon the interaction of (1) hemolysis, (2) compensatory regeneration, and (3) a tendency on the part of the blood-form-

ing tissue to produce immature forms. A somewhat similar line of reasoning is espoused by H. Lehdorff (Schweiz. med. Wchnschr. 65:333 (Apr. 13) 1935), who classifies under the term "erythroblastic disease" the following: fetal erythroblastoses, congenital hemolytic jaundice, Cooley's anemia, and even the almost defunct von Jaksch anemia. He takes the rather extreme view that the erythroblasts present in these cases are evidences, not of excessive bone-marrow activity, but are abnormal blood cells, abnormally found in the marrow and of no value as oxygen carriers in the blood.

#### "SPLENIC ANEMIA." — *Types.*

—As commonly stated, the term splenic anemia means very little and is more often a hindrance rather than a help in diagnosis and treatment. There is literally a host of conditions in which, together with splenic enlargement, anemia is present. In fact, it is decidedly unusual to have splenic enlargement without some degree of anemia. The term "splenic anemia" has, therefore, been applied to about every condition in which splenomegaly is present: typhoid fever, malaria, syphilis of the spleen and liver, chronic infectious processes especially in children, cirrhosis of the liver, amyloidosis, Gaucher's disease, myelogenous leukemia, Hodgkin's disease, lymphosarcoma, etc. That there is a condition distinct from cirrhosis of the liver, primary in the spleen, characterized by splenomegaly, anemia, leukopenia, and without etiological background, is seriously open to question, despite the popularity of the now synonymous terms splenic anemia and Banti's disease. The later R. C. Larrabee analyzed 47 cases which most physicians might have called Banti's disease and in which an etiological factor was not readily discernible. In 14 of these cases, the etiological factor was never discovered; in the

other 33, the following factors were observed: alcoholic cirrhosis, toxic cirrhosis, syphilitic cirrhosis, other types of cirrhosis, hepatic abnormalities not cirrhosis, adhesions, congenital heart, ptosis of the spleen. In about one-half the cases, cirrhosis of the liver was present and the splenomegaly in most, if not all, was due to various lesions interfering with the outflow of blood from the spleen. The changes in the spleen were interpreted by the pathologist (F. B. Mallory) to be due to long-continued passive congestion.

Similar views are presented in a paper by L. M. Rousselot (J. A. M. A. 107: 1788 (Nov. 28) 1936), who studied 31 cases presenting splenomegaly, anemia, leukopenia, often intestinal hemorrhages, and sometimes ascites. These cases comprised a heterogeneous group consisting of 9 cases of Laennec's cirrhosis, 2 of unclassified cirrhosis, 2 of schistosomiasis infestation, 2 of thrombosis of the splenic vein, 1 of cavernometous transformation of the portal vein, and 15 in which the obstructive factor was not demonstrated. The feature stressed by this author is the hypertension in the portal circulation, which is due to an "obstructive" factor either demonstrable or speculative. Splenic venous pressure determinations in a few cases gave higher readings than in the peripheral venous circulation. The results of splenectomy in these cases are presented. This major procedure should be avoided when hematemesis has already occurred, and also when there is marked involvement of the liver. The best results of **splenectomy** occurred in those cases in which an obstructive factor in the portal circulation could not be demonstrated: in 10 of 15 of these cases, the patients were alive and well from 4 to 10 years after operation. Concomitant with clinical improvement, there was usually a rise in the various blood values.

**Pathology.**—Paul Klemperer (Am. J. Clin. Path. 6:99 (Mar.) 1936) in a very important paper on the pathologic anatomy of splenomegaly calls attention to the fact that mere enlargement of the spleen does not necessarily indicate primary involvement of that organ, since enlargement occurs in a host of varied conditions and the spleen is an organ in which large numbers of reticulo-endothelial cells are concentrated. Klemperer feels that such vague diagnoses as Banti's disease and splenogenous anemias should be abolished. It is at present impossible to classify the various disorders associated with splenic enlargement on etiological or physiological grounds, so that a "morphologic-pathogenetic" classification might be best. According to this method, splenomegaly may be classified as (1) inflammatory (bacterial endocarditis, malaria, syphilis); (2) infiltrative (Gaucher's disease, etc.); (3) hyperplastic (polycythemia, purpura, etc.); (4) neoplasms; (5) cysts; (6) chronic disturbances of blood circulation, as in obstruction of the portal or splenic veins, cirrhosis of the liver. In the latter condition, the spleen was enlarged in 79 per cent. of the cases. Klemperer very carefully outlines Banti's original conception of a "new" disease characterized by splenomegaly and later by cirrhosis of the liver, and concludes that neither the clinical picture nor the histologic splenic lesions are specific but may occur in many other conditions. He makes this cogent observation: "The alleged favorable results of splenectomy at this (the early) stage cannot be used as a basis for diagnosis of this disease because there is no evidence to prove that the progress of the disease was actually arrested."

**Treatment.**—Splenectomy in cases of "*chronic congestive splenomegaly*" (to use Larrabee's term, which seems

a good one) was discussed at length at a symposium on splenectomy held at the 1935 meeting of the American Medical Association. C. A. Doan, G. M. Curtis, and B. K. Wiseman (J. A. M. A. 105:1567 (Nov. 16) 1935), although noting the dangers inherent in the operation in late stages of the disorder, made a plea for its use in early cases. They felt that splenectomy might either delay or even prevent the progress of the disease. It is difficult, as brought out in the discussion of this paper, to bring oneself to splenectomy in an early case, in which diagnosis is so difficult; again, it is well-known that many cases survive for 5 to 20 years after an initial hematemesis from esophageal or gastric varices in which nothing has been done. The statistics for splenectomized and nonsplenectomized cases in a comparable series would probably show very little difference, and might be in favor of the nonsplenectomized group (which has not suffered the hazards of the operation).

**GLANDULAR FEVER (INFECTIOUS MONONUCLEOSIS).**—This is probably one of the most commonly overlooked diseases in general practice. It is usually called "grippe," since it presents itself with fever, headache, and sore throat. Glands not ordinarily being looked for are frequently missed. The diagnosis should be suspected in a youngish individual who develops an irregular, rather slight fever which tends to remit at intervals, and complains of headache, some sore throat, at times even of abdominal pain. H. L. Tidy, C. A. McKinlay, and B. K. Wiseman present the various clinical features. An interesting symptom is severe abdominal pain, presumably due to enlarged mesenteric glands, and often misdiagnosed as appendicitis. The super-

ficial lymph nodes are always enlarged, especially those of the upper cervical, submaxillary, and suboccipital areas. It is curious, but none the less true, that in almost every case the left-sided cervicals and supraclaviculars are much more prominent than those on the right. The *diagnosis* is made in most cases by physical examination alone, which shows an individual with fever, general lymph node enlargement, yet who does not appear at all ill. There is no anemia and no bleeding, as seen in acute leukemia. Diagnosis is made positive by examination of the blood smear, which shows extreme lymphocytosis, the lymphocytes being of many types: large, extremely large, those with indented nuclei, with heavy blue cytoplasm, etc. The bizarre blood picture is quite in contrast with that seen in acute leukemia, in which a monotonous blood picture is quite the rule. Wiseman states that supravital preparations are superior to the ordinary stained smears because certain characteristics of nucleus and cytoplasm are lost in the latter. H. Downey and J. Stasney (*Folia hæmat.* 54:417, 1936) describe carefully the pathology of the lymph nodes in the disease and point out that although occasionally the node resembles the picture of leukemia, there is never the complete loss of structure seen in advanced cases of leukemia and no invasion of the capsule. The reticulum is generally hyperplastic with transformation of some of the cells to lymphocytes. The blood picture is, of course, the end-result of the extreme hyperplasia found in the lymph nodes and indicates "a reaction that is more or less leukemoid in nature to an infective, toxic, lymphotropic agent."

In the REVIEWER's hands, diagnosis from the stained blood smear alone has proven entirely satisfactory, and the recently introduced heterophile agglutin-

ation test has proved more of scientific interest than a diagnostic help. The test does not seem to be positive in every typical case; it is, of course, satisfying (as absolutely ruling out leukemia) to obtain a strongly positive test. In recent articles by Stuart, Burgess, Lawson, and Wellman, C. A. Stuart, J. Tallman and E. Brintzenhoff (*J. Immunol.* 28:85 (Feb.) 1935), G. H. Bailey and S. Raffel (*J. Clin. Investigation* 14:228 (Mar.) 1935) and others, in which is discussed the theoretical significance of the agglutination phenomenon, no hint has as yet been obtained regarding its cause. It is likely that from it will some day come information about the etiology of the disease. In this regard, Bailey and Raffel (*Ibid.*) state that the agglutination reaction is probably the specific response to an antigen having a factor in common with a thermostable component of sheep and ox red cells, a certain strain of *B. Welchii*, and possibly horse kidney. E. M. Butt and A. G. Foord suggest a quick microscopic test by using one loopful of blood serum to be tested mixed with 4 loopfuls of a 2 per cent. suspension of sheep's red cells in a hanging drop preparation. In blood from infectious mononucleosis almost immediate agglutination takes place. Some cases are associated with severe fusospirochetal infections (Vincent's angina), and for these, as suggested by Wiseman, **peroxide gargles** and 1 or 2 intravenous injections of **neoarsphenamine** hasten healing. Most cases, however, require nothing but symptomatic treatment. A feeling of "lack of pep" may persist for a month to several months after fever and lymphadenopathy have subsided. The blood picture gradually returns to normal within 2 or 3 months; it is well to know that a second infection occurring within a year may be associated with lymphocytosis.

**AGRANULOCYTOSIS.**—During the past year, enough data have been accumulated regarding this disease to permit of a summary of most of its important aspects.

**Etiology.**—When the disease was first described (1922) and for about 10 years thereafter, very little was known about its cause. Infection, a peculiar metabolic disturbance, some endocrine abnormality, "allergy" were all implicated. Beginning with 1931 articles began to be written implicating various drugs, principally *amidopyrine* (Kracke, Madison, and Squier). The relationship etiologically between amidopyrine and the disease became quite evident following a large series of articles from American and various European sources. Other drugs, notably *dinitrophenol*, have also been implicated (Dameshek and Gargill). Cases have recently been reported following the use of a drug related to amidopyrine (novaldin) by J. E. Benjamin and J. B. Biederman (J. A. M. A. 107:493 (Aug. 15) 1936); following cinchophen and after the use of quinine. It was naturally brought out that amidopyrine and the various sedative mixtures associated with amidopyrine (*allonal*, *peralga*, etc.), although they were being used in tremendous amounts, rarely brought about the disease. The possibility of "allergy" was suggested by several authors. In a study of the various mechanisms involved, W. Dameshek and A. Colmes (J. Clin. Investigation 15:85 (Jan.) 1936) subjected 4 patients who had recovered from the disease to intensive study. All 4 when given from 5 to 50 grains (0.3 to 3.24 Gm.) of amidopyrine by mouth developed first severe headaches and malaise, then striking reduction in white cells and granulocytes, and finally necrotic lesions of the mouth, tongue, and throat. Patch tests, scratch tests, intradermal tests with amidopyrine

solution were all negative, but when the drug was first "aged" with blood serum for several days and the resultant mixture injected intradermally, striking skin reactions occurred, the controls being negative. This indicated that a definite allergic condition was present and that there was a drug-protein linkage such as had been demonstrated with other chemicals chiefly by Landsteiner. Not only did skin reactions occur, but 2 of the 3 patients tested promptly developed severe agranulocytosis, although only approximately a few milligrams ( $1\frac{1}{12}$  grain) of amidopyrine had been injected. This definitely and conclusively showed the extreme hypersensitivity, idiosyncrasy, or allergy of certain sensitive individuals to the drug amidopyrine, and indirectly explained why the great majority of individuals taking this drug failed to develop the disease. It was now possible to piece together the physiological and pathological principles involved.

**Pathology and Physiological Pathology.**—After many preliminary reports by many writers, which were often actually contradictory, a number of reports were published by different investigators all of whom agreed on essential particulars. Fitz-Hugh and Krumbhaar coined the term "maturation arrest" to indicate the condition of the marrow at the height of the disease: a marrow crowded with primitive white cells which were apparently prevented from or unable to mature to normal polymorphonuclears. This report was soon confirmed by Jaffe, Custer, and Parker, Darling, and Jackson. All of these authors emphasized that although peripheral blood was barren of polymorphonuclears, the marrow was crowded with immature leukocytes. K. Rohr (Folia hæmat. 55:305, 1936), in a comprehensive investigation studied the bone-marrow during life and corre-

lated it with the blood picture. Rohr used the method of bone-marrow puncture, employing a hollow needle and was thus able to do frequent punctures during the course of the disease. He also produced agranulocytosis experimentally in several patients by giving them amidopyrine and observed the bone-marrow before and after administration of the drug. A maturation arrest of the bone-marrow granulocytes developed and Rohr concluded that this was an anaphylactic reaction, with the bone-marrow acting as the "shock organ." P. Plum (Ugesk. f. laeger 98:91 (Jan. 30) 1936) did the same experiment in 3 patients and concluded that administration of amidopyrine by mouth to amidopyrine-hypersensitive persons produces an extraordinary severe and protracted inhibitory effect on granulocytopoiesis. The REVIEWER has shown (unpublished data) that giving amidopyrine in large doses to a group of normal individuals will induce in many of them a reduction in granulocytes and in white cells; when the drug is discontinued, a marked jump in leukocytes and in granulocytes usually occurs ("release phenomenon"). All of these pieces of evidence indicate quite clearly (1) that certain individuals have developed a hypersensitivity to amidopyrine; (2) that the hypersensitivity is manifested by severe shock to the bone-marrow, with particular reference to the production or maturation of the bone-marrow white cells. In the presence of maturation arrest of granulocytes; (3) the peripheral blood becomes depleted of polymorphonuclear cells. After this has gone on for a few days, (4) the effects of agranulocytosis become clinically manifest: high fever, malaise, prostration, necrotic lesions of the mucous membranes. In the absence of granulocytes, (5) secondary sepsis is easily possible because of the presence normally within the mouth and other parts

of the body of bacteria; septicemia may develop.

**Diagnosis.**—The diagnosis of the typical case is relatively simple. There is marked prostration and relatively little to show for it beyond the presence of lesions of the gums, throat, or other mucous membranes. If petechiæ are present and anemia is marked, it is likely that agranulocytosis is not present, but rather some disease entity in which, although the granulocytes are very much reduced, the bone-marrow as a whole is affected and there is anemia and thrombocytopenia as well. This combination of anemia, leukopenia, and thrombocytopenia may be due to aplastic anemia (benzol, arsenic, gold, etc.), to carcinoma or lymphosarcoma metastasizing widely into the bone-marrow, or to leukemia or generalized Hodgkin's disease overrunning the marrow. The *differential diagnosis* of these conditions is best made by bone-marrow biopsy, as the REVIEWER has repeatedly pointed out (W. Dameshek: Am. J. M. Sc. 190: 617 (Nov.) 1935). Agranulocytosis itself is usually associated with only slight reduction, if any, in the red cells and without reduction in the platelets.

**Treatment.**—Although there is a good deal of disagreement among different observers, the only consistent therapeutic results which have been obtained have followed the use of certain nucleic acid derivatives. Chief among these are a mixture of pentose nucleotides (**pentnucleotide**) given in 10 c.c. ( $2\frac{1}{2}$  drams) doses several times daily, intramuscularly, and **adenine sulphate** given in 1 to 2 Gm. (15 to 30 grains) doses, intravenously, dissolved in 50 to 100 c.c. ( $1\frac{2}{3}$  to  $3\frac{1}{3}$  ounces) of **normal salt solution**. The REVIEWER prefers the latter medication, because it seems more rapidly effective and its use is not attended with reactions. Within 48 to 60 hours, immature granulocytes will

usually appear in the circulation, to be followed later by an increase in the total leukocyte count. If the diagnosis is too delayed, therapy will be ineffective. Jackson and Parker found that 67 per cent. of 103 patients recovered; whereas prior to the introduction of this method of therapy, the rate of recovery was only from 10 to 25 per cent.

**LEUKEMIA.—Types.**—The case reports concerning leukemia bulk large in hematological literature and every year more and more cases seem to be observed. Yet the outlook remains just as tragic as ever. Most investigators feel that the disease represents a highly malignant generalized neoplastic condition of one of the three blood-forming organs: the bone-marrow, the lymphoid system, and the reticulo-endothelial system. It is very likely that the localized neoplasms of these organs (chloroma, lymphomata, reticuloma, etc.) are very closely related to the leukemic, or generalized conditions. The malignant character of leukemia and its relationship to localized neoplasms are well brought out in an experimental study in rats by J. Furth (J. Exper. Med. 61:423 (Mar.) 1935): an emulsion of spleen from a mouse dying of myeloid leukemia when injected into other mice at times produced leukemia, at times tumors, and at other times a combination of tumor and leukemia. The type of condition which developed was dependent upon the route of entry, the resistance of the host and the character of the cells injected. Both "acute" and "chronic" types of leukemia developed. In another paper, J. Furth, H. W. Ferris and P. Reznikoff (J. A. M. A. 105:1824 (Dec. 7) 1935) point out the close clinical and hematological similarities between leukemia in man and leukemia in mice and emphasize again the neoplastic characteristics of leukemia and its relationship to such

localized tumors as lymphosarcoma. Furth feels that to classify leukemia into acute and chronic varieties is arbitrary, since they both are the same disease with different growth tendencies.

What starts off the irreversible leukemic process is not known. Some hint might be obtained from those cases of leukemia which occur in workers exposed to much x-radiation. In a very interesting (Belgian) letter in the (*Ibid.* 104:1921 (May 25) 1935) the remarks of Maisin to the Belgian Society of Radiology anent the morphologic changes in the blood of radiologists are reported. According to the correspondent, Maisin states that 25 per cent. of radiologists are affected with lymphoid leukemia (!!). Two Belgian radiologists have died of leukemia. Maisin states further that close attention to protection from the x-rays is imperative, particularly in therapy. L. F. Craver (*Ibid.* 105:1820 (Dec. 7) 1935), in discussing the etiology of cancer, refers to work by several authors concerning the development of various types of blood cell tumors and leukemia in mice following injections of such chemicals as indole, tar, etc.

In a lengthy and very important paper B. K. Wiseman (Ann. Int. Med. 9:1303 (Apr.) 1936) discusses lymphopoiesis, lymphatic hyperplasia, and lymphemia with "fundamental observations concerning the pathologic physiology and interrelationships of lymphatic leukemia, leukosarcoma and lymphosarcoma." After a discussion of normal lymphopoiesis, Wiseman takes up the history of the development of concepts of the lymphoid hyperplasias and divides them into 4 main types: lymphatic leukemia, lymphatic pseudoleukemia, leukosarcoma, and aleukocythemic (aleukemic) lymphatic leukemia. "*Lymphatic pseudoleukemia*" is the same pathologically as lymphatic leukemia except that the cells do not get

out into the blood-stream (are "screened out"). *Leukosarcoma* represent a sarcomatous disorder of lymphoid tissue, with the formation of pathological lymphocytes which get out into the blood-stream and give the picture of leukemia. *Aleukocythemic (aleukemic) lymphatic leukemia* is a disorder in which the cells are lost from the blood-stream into the tissue spaces and tend to overgrow the blood-forming organs. Wiseman concludes that there are 2 types of lymphatic leukemia: (1) a *metabolic form*, which is probably more common and in which the cells are normal in type, but they do not mature as they normally should; and (2) a *neoplastic form*, which tends to overrun tissues in typical malignant form. The concepts of Wiseman are based on much study and observation and, although in many respects unorthodox, are worthy of careful consideration.

**Diagnosis.**—The diagnosis of leukemia may either be difficult or easy. With the blood filled with large numbers of cells, almost all immature, the diagnosis should be made in every instance, whether or not the exact type of cell—myeloblast, lymphoblast, or monocyte—is differentiated. In the presence of a normal or even a low white cell count and anemia (at least one-half the cases present these features) the diagnosis may be more difficult. N. Rosenthal and W. Harris discuss the difficulties in diagnosis from a review of 455 cases seen over a period of years. The important characteristic feature they feel is the persistent relative or absolute increase in number of mature or immature white cells. R. R. Kracke and H. Garver emphasize the importance of recognizing the immature cells in the disease as well as the macrocytosis of the red cells which at times causes confusion with pernicious anemia. In children, particularly, the diagnosis may

often be very difficult, as brought out by A. F. Abt, since leukemia may be confused with such totally different conditions as diphtheria, scurvy, endocarditis, rheumatic fever, von Jaksch anemia, Cooley's anemia, etc. What strikes the REVIEWER in seeing these cases is the blind faith so often placed by physicians in the hematological reports of technicians. [This illustrates again the power of the written word, particularly on a laboratory report.] With few exceptions, technicians seem to call all types of cells with deep blue cytoplasm lymphocytes or large mononuclears, whether they are lymphoblasts, myeloblasts or histiocytes.

Interest in *monocytic leukemia* continues intense, as these cases are more readily recognized. J. Levine, I. E. H. Whitby and J. M. Christie and also K. Kato (J. Lab. and Clin. Med. 20: 1243 (Sept.) 1935) agree that this type of leukemia is probably much more frequent than has heretofore been suspected.

The *neurological changes* which occur in leukemia are often quite interesting and have been analyzed by R. S. Schwab and S. Weiss. I. Goldstein and D. Wexler (Arch. Ophth. 13:26 (Jan.) 1935) studied the fundus oculi carefully in 11 cases. In most instances the changes are minimal, in an exceptional case quite striking. In the REVIEWER's experience, the most marked changes occur in acute lymphatic leukemia, when the retina may often be seen to be thick, edematous, and shiny. The bone changes in leukemia have been the subject of several articles. H. P. Doub and F. W. Hartman state that "moth-eaten" areas in the bones on the x-ray plate together with pin-point areas of decalcification in the flat bones are suggestive of myeloid or lymphatic types. L. F. Craver and M. M. Copeland found bone changes in about 7 per cent. of 86 cases of lymphatic



leukemia; in only 1 of 84 cases of myelogenous leukemia. Children are especially prone to bone changes, as noted by C. E. Snelling and A. Brown, who found changes in 8 of 12 cases.

**Treatment.**—Very little advance has been made in treatment of this dread disease. Isaacs analyzes the 3 main types of therapy used: **X-rays, transfusion of blood, and arsenic.** This investigator advocates the minimum number (4 or less) of doses that are necessary to produce the desired result. He states that small repeated doses shorten the remissions and hasten the period in which most of the cells appear in the blast stages. H. Langer advocates **treatment over the spinal column** in order that the paravertebral ganglia might be irradiated and thus depress an (highly speculative) overactive sympathetic nervous system. The latter system has been previously related to leukemia: Friedgood some years ago found reduction in basal metabolic rate and in white cell count following **Lugol's solution**—this was interpreted as a possible action on an overactive sympathetic nervous system. W. Dameshek, D. D. Berlin and H. L. Blumgart more recently performed **thyroidectomy** in a case of *chronic lymphatic leukemia* showing extreme hypermetabolism with excellent results.\* M. C. G. Israels treated 5 cases of *chronic lymphatic leukemia*, first with **Lugol's solution** then with **x-rays**. He concluded that there was no relation between lymphatic leukemia and hypermetabolism and, therefore, thyroidectomy was not at present justified. N. Rosenthal and W. Harris consider that **radiotherapy** is of most value in *chronic myeloid* and *lymphoid leukemia*, although results were temporary and resistance apt to

develop. In contradistinction to most writers, Rosenthal and Harris feel that **radiotherapy** is justified in *acute leukemia*.

D. J. Stephens and J. S. Lawrence (Ann. Int. Med. 9:1488 (May) 1936) again bring out the value of properly controlled treatment with **Fowler's solution** which is of chief value in *chronic myelogenous leukemia* either as an adjuvant to **x-ray therapy** or as a single therapeutic agent. The drug is given in rapidly increasing doses until toxic symptoms appeared: nausea, vomiting, diarrhea, swelling of the eyelids, and generalized itching. In many cases, prompt amelioration of symptoms, signs, and blood picture appeared. The REVIEWER has seen occasional good results following the exhibition of this type of therapy, but it is usually necessary to discontinue it on account of toxic symptoms (which are often worse than the disease itself). Sudden discontinuance may result in the development of herpes zoster. When x-ray therapy is not available, **Fowler's solution** is of distinct value, but only in *chronic myelogenous leukemia*; it is of no value in chronic lymphatic leukemia or in Hodgkin's disease.

**NEOPLASMS OF WHITE CELLS.**—H. P. Doub and F. W. Hartman presented cases of lymphosarcoma terminating as lymphatic leukemia, chloroma (myelosarcoma) and Hodgkin's disease. Callender's classification is also utilized by Doub and Hartman. There are 3 types of white cells (granulocytes, lymphocytes, monocytes) derived from the 3 blood-forming organs (bone-marrow, lymphoid tissue, and reticulo-endothelial system) and which are subject to either general or local proliferation. General proliferation is leukemia; local proliferation results in a tumor. There are bone-marrow, lym-

\*This patient is still alive and well after 3 years. One year after striking improvement had occurred, all of the symptoms and signs were reinduced by large doses of thyroid.

phoid, and reticulo-endothelial tumors. These may be highly malignant (sarcoma) or only slightly malignant. Gradations in types of malignancy are frequently seen. An incomplete list of these tumors is as follows:

Bone-marrow.—Myelosarcoma (chloroma), myeloma.

Lymphoid Tissue.—Lymphosarcoma, lymphoma and plasmacytoma (multiple myeloma).

Reticulo-endothelial Tissue.—Reticulum cell sarcoma and Hodgkin's disease, reticulo-endothelioma.

It is noted from this list that "multiple myeloma" is a misnomer, and is in reality a tumor of lymphoid cells (plasma cells) which, like most blood cell tumors, tend to invade bone. It is also noted that Hodgkin's disease is included among the reticulo-endothelial tumors, where many pathologists now place it.

Regarding *Hodgkin's disease*, L. Potter states that there is a proliferation of reticulum cells along both normal and abnormal lines. Some of the abnormal cells develop into typical "Hodgkin" cells which are very large with basket-shaped nuclei, either single or multiple in type. According to Potter, Hodgkin cells are never found except in Hodgkin's disease. G. M. Roth and C. H. Watkins (Ann. Int. Med. 9:1365 (Apr.) 1936) investigate again the question of the leukocyte picture in Hodgkin's disease and conclude that there is no specific diagnostic picture. When the disease becomes advanced, there is a definite increase in polymorphonuclear cells and a decrease in lymphocytes. This is apparently due to overcrowding of the lymphoid tissue with the Hodgkin process, with consequent destruction of lymphoid-producing cells. D. H. Rosenberg and L. Bloch (J. A. M. A. 106:1156 (Apr. 4) 1936) investigated the *Gordon test for Hodgkin's disease*. This test consists of the injection into the cerebrum of rabbits or guinea-pigs a sterile suspension prepared from biopsied

lymph-nodes. In 3 cases which the authors studied, the test was positive in 2 early cases and negative in 1 chronic case; 3 abnormal lymph-nodes, not Hodgkin's, gave negative tests. The rationale of the test has not yet been worked out.

H. Jackson, Jr., F. Parker, Jr., and A. M. Brues (Am. J. M. Sc. 191:1 (Jan.) 1936) present an analysis of 28 cases of "*malignant lymphoma*" (lymphosarcoma) *of the tonsil*. The most prominent *symptoms* initially noted were persistent sore throat, swelling within the throat, and enlargement of the cervical lymph-nodes. In 56 per cent. of the patients, generalized lymphosarcomatosis developed. One patient was, however, alive at 5 years, 2 at 10 years, and 1 free from symptoms 18 years after onset. The *treatment* is persistent **x-ray irradiation**, which is of greatest help when local lymph-nodes are absent at the time of beginning treatment.

A good deal of attention is being paid to "*multiple myeloma*" (*plasmacytoma*) and more particularly to the changes in the blood protein which occur in association with it. A. G. Foord found marked hyperproteinemia in 3 of 4 cases, together with autohemagglutination of the red cells. It is remarked that the findings of either a very high blood protein or of marked rouleaux formation of the red cells, either in smears or in hemocytometers, should make one suspect the presence of the disease. Helene Bürkel demonstrates that in various diffuse and localized disturbances of the bone-marrow the blood protein values do not deviate greatly from the normal. Hyperproteinemia is seen only in "*myeloma*," although it does not occur in every instance of the disorder. A. H. Rosenblum and J. D. Kirshbaum (J. A. M. A. 106:988 (Mar. 21) 1936) report a very interesting case of *multiple myeloma* in which, although Bence-Jones

protein was not present in the urine, still there was a marked increase in an atypical proteose. This case was complicated by the presence of severe amyloidosis associated with the nephrotic syndrome.

**HEMORRHAGIC DISEASES**  
(Hemorrhagic Diathesis.) — *Classification.* — It is customary to group under the designation of hemorrhagic diathesis a number of disorders in which the only common factor is the tendency to abnormal bleeding. The following classification is offered, since it has proved useful in teaching and in the clinic.

1. Disturbances of Clotting Mechanism:  
Hemophilia; pseudo-hemophilia; increased coagulation time of jaundice.
2. "Purpura":
  - (a) With deficiency in blood platelets (thrombocytopenic form):
    - (1) "Primary," "idiopathic" or "essential."
    - (2) Secondary to involvement of bone-marrow by a destructive process:
      - Chemical — benzol, arsenic, x-rays, radium, etc.
      - Carcinoma and sarcoma.
      - Leukemia.
      - Gaucher's disease.
  - (b) Without deficiency in blood platelets ("vascular" form):
    - Anaphylactoid, senile, toxic, nutritional, scorbutic, etc.
3. With a well-substantiated vascular defect:  
Hereditary hemorrhagic telangiectasis; other forms of telangiectasia.

**DISTURBANCES OF CLOTTING MECHANISM.** — *Hemophilia; Increased Clotting Time of Jaundice.* — Despite an enormous amount of investigation, little success has been attained in the elucidation of the defective clotting mechanism in hemophilia. A. J. Patek, Jr., and R. P. Stetson (J. Clin. Investigation 15: 531 (Sept.) 1936) seem, however, to be

making progress in this difficult field. These authors state that "the one abnormality constantly found in hemophilia is an inability of the blood to coagulate in a normal manner," a defect demonstrable in the prolonged clotting time. They, therefore, set out to find what it was that caused this prolongation. It was assumed further that normal blood contains a substance which either supplies a clotting factor lacking from hemophilic blood or which counteracts a mechanism inhibiting coagulation of the blood in hemophilia. The problem was to find this substance, and to do this necessitated abandonment of much of the previous dead wood in the numerous theoretical concepts of the mechanisms of coagulation. The coagulation time as determined by a standard technic was tested in normal and hemophilic blood before and after the use of various test substances. From these tests they concluded that "there is a substance in normal blood which in small quantity effectively reduced the clotting time of hemophilic blood, both *in vitro* and *in vivo*; this substance is present in platelet-free plasma and in the plasma of thrombopenic purpura. Further experiments demonstrated that the platelets of hemophilia were normal and the clotting factor of normal plasma had nothing whatever to do with the platelets or their degradation products.

J. S. Gray and A. C. Ivy (Am. J. Digest. Dis. and Nutrition 2: 368 (Aug.) 1935) studied the *serum calcium* in cases of *jaundice* and found that there was no change in either the diffusible or non-diffusible forms. From this, they inferred that the calcium metabolism was not responsible for the increased bleeding in jaundice, but that it was probably related directly to the degree of liver damage. [This might link up with a fibrinogen defect, as postulated by Patek and Stetson, and which has been known

to be present in severe liver damage.] A. J. Quick, M. Stanley-Brown and F. W. Bancroft set out to find the coagulation defect in cases of jaundice which they thought resided in an alteration in the prothrombin content of the blood but came to no definite conclusion.

**Treatment.**—**Transfusion of whole blood** or of **normal blood plasma** is the best known therapeutic measure available for hemophilia. Patek and Stetson have already demonstrated that relatively small amounts of blood plasma kept at ice-box temperature are effective in rapidly shortening the clotting time in cases of hemophilia. To *forestall bleeding* in cases of severe *jaundice* which necessitate *operation*, E. S. Judd, A. M. Snell and M. T. Hoerner (J. A. M. A. 105:1653 (Nov. 23) 1935) recommend the use of repeated **transfusions** preferably given before operation. Other methods for shortening the clotting time of the blood are still being tried. R. C. Eley, A. A. Green and C. F. McKhann (J. Pediat. 8:135 (Feb.) 1936) gave an **extract of human placenta** to 15 children with hemophilia, either orally or by intramuscular route. Eleven of the 15 cases showed a satisfactory response, with reduction of the clotting time to normal limits. R. G. MacFarlane (St. Barth. Hosp. Rep. 68:229, 1935) recommends the use of **Russel's viper venom** for application locally to stop bleeding in cases of hemophilia. This venom was obtained from vipers in the collection of the Zoological Society of London and was effective in clotting hemophilic blood in a concentration of 1 in 1 billion within 6 minutes. It was used locally on external wounds or to the gums after dental extractions with success in 5 of 7 cases. B. Barnett (Proc. Roy. Soc. Med. 28:1469 (Sept.) 1935) reported similar results with the same venom applied locally in 6 cases of hemophilia. These results are similar to those obtained by

S. Rosenfeld and S. E. Lenke (Am. J. M. Sc. 190:779 (Dec.) 1935), who used the venom of the Australian tiger-snake which readily clots 12,800,000 times its weight of heavily citrated or oxalated blood. These authors find that **tiger-snake venom** is superior to Russel viper venom in many important respects. W. A. Timperley, A. E. Naish and G. A. Clark (Lancet 2:1142 (Nov. 14) 1936) report the discovery of a **nonprotein substance derived from egg white** which when given intravenously to cases of hemophilia shortened the clotting time and stopped further progress of symptoms.

**Purpura.**—It is possible that bleeding does not occur under the skin in the form of petechiae or ecchymoses unless there is an associated (hypothetical) vascular defect. It is also possible that these hypothetical vascular defects may be initiated by the same stimuli which produce the reduction in blood platelets. Speculations aside, however, it is usually possible to divide purpura into 2 main types: (1) with platelet deficiency; (2) without platelet deficiency.

**THROMBOCYTOPENIC PURPURA.**—*The So-called Idiopathic or Essential or Primary Type.*—*Etiology.*—The more disorders of various types are studied, the more disinclination is there to call anything essential or primary or idiopathic. Causes are rapidly being discovered for the "primary" anemias of another decade and the same sort of evolutionary change seems to be developing with thrombocytopenic purpura. Thus, in recent years the sedative *sedormid* has been implicated in an increasing number of cases (E. P. Boas and L. A. Erf: New York State J. Med. 36:491 (Apr. 1) 1936; S. M. Peck, N. Rosenthal and L. A. Erf: J. A. M. A. 106:1783 (May 23) 1936). *Neoarsphenamine* has again been implicated (E. H. Falconer, N. N. Epstein

and G. K. Wever (Arch. Int. Med. 58: 495 (Sept.) 1936) in 3 cases which developed severe toxic constitutional reactions accompanied with purpura hemorrhagica. These authors felt that there was a distinct relationship between the nitrotoxic crises of the arsphenamines and the development of thrombocytopenic purpura hemorrhagica. Other drugs which have been incriminated as the probable causes of certain cases of purpura are quinine, chrysarobin, nirvanol, gold, benzene (Cf. Patek's Review in Am. J. M. Sc. 191:723 (May) 1936). It is likely that the development of purpura in these cases is in the nature of an allergic reaction, the marrow becoming involved by the "toxic" factor in much the same way as the leukocytes are involved in agranulocytosis (*q. v.*). The observation by the REVIEWER of a series of 4 cases of thrombocytopenic purpura following major operative procedures leads to speculation concerning the possible rôle of *barbiturate preparations* so widely used as preoperative medications.

Despite observation of cases in which an etiological factor was present, the majority of the cases present no discernible causative mechanism. In those cases occurring usually in girls and developing at about the time of onset of the menstrual cycle, a possible *endocrine factor* may be postulated. This is strengthened by the fact that in certain cases the platelet count becomes greatly diminished with the menstrual periods. G. R. Minot (*Ibid.* 192:445 (Oct.) 1936) reports a group of 3 cases occurring periodically with menstruation and discusses the possibility of an altered endocrine function.

In the "idiopathic" cases, there is a great deal of speculation regarding the mechanisms involved. In common with many authors, C. A. Doan, G. M. Curtis and B. K. Wiseman (J. A. M. A.

105:1567 (Nov. 16) 1935) put the big question: Does the spleen inhibit the formation of platelets in the bone-marrow or does it destroy them overly fast? They do not attempt to answer the question completely, but they bring out the idea that the spleen holds the key position in the so-called hemolytotoxic equilibrium (a term first used by Krumbhaar in 1923). Several investigators have attempted to reproduce the disease experimentally in animals by the use of antiplatelet extracts. Thus, L. M. Tocantins (Arch. Path. 21:69 (Jan.) 1936); Ann. Int. Med. 9:838 (Jan.) 1936) induced thrombopenic purpura in dogs by the use of an antiplatelet serum. With the production of a very low platelet count, several tests were performed: bleeding time, clot retraction, tourniquet test, etc. The correlation between the level of the platelet count and the bleeding time was not as great as that with the degree of clot retraction.\* E. Filo (Sang 10:704, 1936) produced thrombocytopenia in rabbits by the use of a guinea-pig antiplatelet serum. He then studied the bone-marrow and found that the megakaryocytes were still present in normal numbers along with various types of nuclear changes. The bleeding time was found prolonged in all the experiments. Removing the spleen had no effect on this type of purpura. A. Krjukof (*Ibid.* 9:363, 1935) reports a case of thrombocytopenic purpura with bone-marrow biopsy; although there were no platelets in the peripheral blood, the marrow showed many megakaryocytes.

*Diagnosis.*—Although their article is not strictly concerned with purpura, but

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\* The bleeding time is obtained by puncturing the ear with a large bore needle and measuring the time for bleeding to stop; normal is 1 to 3 minutes; increased with diminution in platelets. Retraction of the clot normally occurs in a test tube when blood is allowed to coagulate; with deficiency in platelets, the clot retracts very slightly if at all in 24 hours.

with a careful study of latent and clinical scurvy, I. S. Wright and A. Lilienfeld (Arch. Int. Med. 57:241 (Feb.) 1936) make an important contribution relative to the diagnosis and study of these cases in the form of a standardized *tourniquet test*. It is important to know in a given case of purpura (1) whether the tourniquet test is positive and (2) how strongly positive it is. Mere application of a tourniquet for several minutes gives only rough information. Wright and Lilienfeld recommend that a blood-pressure cuff be applied to the arm half way between systole and diastole for a period of 15 minutes. The number of petechiæ appearing in a circle 2 cm. in diameter (4 cm. below the bend of the elbow) is noted. Up to 7 petechiæ is normal. The number is recorded and thus the test becomes an objective one (of capillary resistance) and can be recorded and charted from day to day according to the patient's course.

*Treatment.*—With reference to therapy, **splenectomy** continues to hold its place as a reliable, although radical, form of treatment. Doan, Curtis, and Wiseman (*loc. cit.*) advance a great deal of clinical data to show the value of this procedure. In a very careful follow-up of 21 cases, 10 splenectomized and 11 treated conservatively by various medical measures, D. N. Brown and R. H. E. Elliott (J. A. M. A. 107:1781 (Nov. 28) 1936) make the following summary: "In the splenectomized group 80 per cent. of the cases were vastly improved or arrested, while the same can be said of only 27.2 per cent. of the control series. It will be seen further that under improved but by no means arrested we find 10 per cent. of the operative and 18.1 per cent. of the controls, and that under unimproved or died we find 10 per cent. of the splenectomized and 54.5 per cent. of the non-

splenectomized. In short, we have found 3 times as many excellent results among the operative group as among the controls, and 5 times as many poor results among the controls as among the operative group."

All this is certainly true, but the physician should frankly hesitate before subjecting a patient to the major operative risk (7 per cent. in a large series of cases) of splenectomy and should try the various available "medical" procedures first. S. R. Mettier and R. S. Stone (Am. J. M. Sc. 191:794 (June) 1936) treated 7 patients with the disease by **x-ray therapy** over the spleen. In 6 cases, the platelet count rose to high limits within 24 to 48 hours after beginning treatment. The authors cannot explain the mechanism of the reaction, which is usually a transitory and not a curative phenomenon. Moccasin **snake venom** is, according to S. M. Peck and N. Rosenthal (J. A. M. A. 104:1066 (Mar. 30) 1935), effective in some cases and ineffective in others. H. Lowenburg and T. M. Ginsburg (*Ibid.* 106:1179 (May 23) 1936) produced hypercalcemia in 2 patients (children) by the use of **parathyroid extract** in dosage of 3 c.c. (60 units) given daily subcutaneously. **Calcium gluconate** 10 c.c. (2½ drams) was given intramuscularly at the same time. In both cases, the patients developed severe symptoms of hypercalcemia: apathy, lethargy, and persistent vomiting, associated with a marked increase in the serum calcium. Simultaneously with the development of these symptoms, there was striking diminution in bleeding time, improved clot retraction, and rise in platelet count. This method deserves further trial. Many writers refer to the use of **ascorbic acid (vitamin C)**. Thus, J. R. Dreyfus (Presse méd. 44:589 (Apr. 8) 1936) reports 2 cases in childhood responding

to intravenous **vitamin C**. Many of these reports are uncontrolled and not convincing. In the careful observations of Wright and Lilienfeld (*loc. cit.*) there was no improvement in thrombocytopenic purpura following this method of therapy.

**NONTHROMBOCYTOPENIC PURPURA, VASCULAR PURPURA.**—This type of purpura is apparently due to a defect of the capillary wall, since the platelets are normal, the bleeding time is normal, and clot retraction is normal. The abnormality of the vessel wall may be due to some well-defined cause such as deficiency in vitamin C, a severe allergic reaction, uremia, or may be completely

“idiopathic.” The REVIEWER has seen many women with ecchymotic spots which usually appear about the time of the menstrual period and which are of no significance. **Calcium salts** are of value in these cases. At times, the surgeon is faced with the problem of severe bleeding postoperatively in a patient whose tests (bleeding time, clotting time, platelet count, etc.) are all negative, but whose tourniquet test may be positive. In these cases, it is the REVIEWER’S impression that **antivenin** given in 1 dose of 10 c.c., intramuscularly, and possibly followed by **moccasin snake venom** in rapidly increasing doses, is of distinct benefit.

## DISEASES OF THE KIDNEY

By FRANCIS D. MURPHY, M.D.

Each year brings forth new articles which contribute to a better understanding of the relationship between the clinical features and the pathological physiology of the kidney. Accurate diagnoses and satisfactory methods of treatment are to a large degree dependent upon such added information. A single article on some aspect of Bright’s disease may appear to have small significance. Yet when the contributions of the year are brought together and analyzed, a reader frequently acquires a better understanding of some phase of this disease. Progress in the field of Bright’s disease has been contributed to by workers in many branches of the basic sciences as well as by internists, pediatricists, and surgeons. In reviewing the literature on diseases of the kidney, no effort is made to include all of the articles which have appeared. Only those are reviewed which contribute to certain aspects of the diagnostic and therapeutic problem.

**ACUTE NEPHRITIS.**—There is almost complete unanimity of opinion that chronic nephritis develops from an acute phase which failed to heal completely. With this point of view in mind, studies of acute nephritis, especially in children and adolescents, take on considerable importance. In the Adelaide Children’s Hospital in Australia, M. T. Cockburn (M. J. Australia 2:643 (Nov. 9) 1935) studied 146 cases of acute nephritis. He emphasizes again that acute nephritis may follow any childhood disease, not only scarlet fever, and that tonsillitis is a precursor in 30 per cent. of the cases. Bronchopneumonia was a forerunner in a few cases and as he points out, pneumonia may be a more important cause than realized because the nephritis is not often looked for. Most of the cases occurred in the autumn months when the weather was cold and damp.

In regard to *treatment*, he mentions the removal of tonsils and adenoids in a

series of 50 cases of acute nephritis. The immediate results were an increase of blood and casts in the urine. Occasionally a relapse occurred within 24 hours, which did not appear to prolong the duration of the disease. There were cures in all but two cases operated on and in all but one of those not operated on. He concludes that the **removal of infected foci** plays no important part in the disease.

E. Glanzmann discusses the diagnosis and treatment of various forms of nephritis commonly met with in children. Special consideration is given to functional *albuminuria*, the so-called pedonephritis of Heubner, which some authors have found so frequent as to feel that it cannot really be regarded as a pathologic condition. One author found a slight albuminuria in not less than 12 to 15 per cent. of 3000 school children; another found albuminuria in 27 per cent. of children between 10 and 11 years old, while those between 15 and 16 years old showed in 38 per cent. Albuminuria is more common in the children of rich parents than in those of the poor, and it is more common in girls at puberty than in boys; but, where it has been possible to follow up such children, mortality is no higher than in others; neither do they show any predisposition to kidney disease later in life.

In an article by C. H. Webb on the treatment of acute nephritis in children, 22 cases, all of the postinfectious type, are discussed. Toxemia and cerebral edema were considered the most frequent dangerous manifestations of the disease and he points out that **ample fluid intake** and **salt restrictions** in addition to cerebral decompression by **lumbar puncture** constitute the therapeutic procedures which are best adapted for these cases. The author warns against the use of magnesium sulphate, ammonium chloride, or other diuretics

in the routine treatment of acute nephritis. Webb's experience with this series of cases covered a period of 3 years. Of the 22 patients, 18 had acute glomerular nephritis secondary to acute infections. It is interesting to note that in his table only 1 case of the 22 was preceded by scarlet fever.

W. L. Winkenwerder, N. McLeod and M. Baker (Arch. Int. Med. 56:297 (Aug.) 1935) studied the relationship between infection with *Streptococcus hæmolyticus* and *hemorrhagic nephritis* in 78 cases observed from 1 to 8 years. They point out that patients with acute infections are able to react to the *Streptococcus hæmolyticus* and fortify themselves against infection. This defense mechanism leads to recovery. On the other hand, the patients with chronic infection do not have this power, and, as a result, infection persists and nephritis continues into the chronic stage. Upper respiratory infections were the precursor in 67.6 per cent. of the cases and tonsillitis in 44 per cent. Pneumococcic infections, rheumatic fever, endocarditis, and latent syphilis were comparatively rare. The fact that only 4 cases of nephritis occurred after rheumatic fever is interesting because of the fact that both are due to the hemolytic streptococcus. In the cases of nephritis studied, 62 showed hemolytic streptococcus of the beta type and 5 (all progressive or fatal) of the alpha type. Eleven cases showed neither streptococcus. The great majority of patients who passed into the progressive or fatal stage continued to harbor the organism, while 68 per cent. of the others were free of the streptococcus after the initial stage. The *Streptococcus hæmolyticus* must, therefore, be related to the successive phases of the disease. The seasonal variation in the frequency of hemorrhagic nephritis corresponded with



those periods when respiratory infection was most common.

L. M. Folkers (J. Iowa M. Soc. 25: 552 (Oct.) 1935) points out that there was no sex difference in the incidence of *acute glomerulonephritis* in a series of 68 cases. Respiratory infections were the most common etiological factor and scarlet fever was next in importance. Seventeen cases presented retinal changes in the acute stage. Renal function was poor in 11 of the 26 patients tested and the nonprotein nitrogen was increased in 31 cases. Four of the 7 patients who progressed to the chronic stage and died showed very high blood-pressure during the acute condition. Twenty-three patients were albumin-free on discharge and most of those now well were free of hematuria. The mortality rate in the acute condition was 5 to 10 per cent. and the percentage of serious sequelae was large, the chief one being chronic nephritis. If the disease is acquired early in life, it is less likely to cause permanent damage or become chronic.

The geographical distribution of *acute glomerulonephritis* in North America compared to that of the distribution of acute rheumatic fever and scarlet fever was studied by D. Seegal, E. B. C. Seegal and E. L. Jost (Am. J. M. Sc. 190: 383 (Sept.) 1935) during the years 1910 to 1931 in 24 hospitals in the United States and Canada. Scarlet fever and rheumatic fever were found to diminish progressively from latitude 50-45 degrees to 34-29 degrees. The frequency of acute glomerulonephritis did not vary significantly. Since the hemolytic streptococcus has been called the chief etiological factor in all three diseases, the lack of variation in the incidence of acute glomerulonephritis is not understood. A special study was made in the southern hospitals which proved the hemolytic streptococcus to be the main incitant of the disease.

The *prognosis* in 100 cases of *acute glomerulonephritis* was reported on by A. B. Richter (Ann. Int. Med. 9: 1057 (Feb.) 1936). Ten of the patients died in the acute stage, 5 of the nephritis and 5 of the causative infection. Sixty-two of the survivors were cured and 15 became chronic nephritics. The degree and duration of the albuminuria was found to be of great prognostic significance. In most cases the decrease of albumin in the urine meant healing. Persistent albuminuria meant progression into the chronic form of the disease. If albuminuria lasts a year or longer, the chances of the renal process becoming chronic are 6 to 1.

In a clinical and statistical study of 94 cases of *acute nephritis*, F. D. Murphy, J. Grill and G. F. Moxon emphasize the fact that a severe case may heal completely, while a very mild one may become chronic. The initial attack may be so mild that it is unrecognized until the chronic stage with renal failure sets in. Hypertension, hematuria, and edema do not always appear at the same time and the authors are of the opinion that hypertension may at times be lacking in the acute stage. Slight or no reduction in quality of plasma proteins was found in the initial stage, but the level tended to fall in those cases where the disease became subacute or chronic.

There is a type of acute renal disorder which is receiving, and well deserves, more attention than it has been given in the past. Reference is made to the acute nephritis (or renal disturbance) *following blood transfusion*. A. Tzanck and R. Moline (Paris Méd. 2:308 (Oct. 19) 1935) find that the number of cases in which nephritis follows blood transfusion is sufficiently large to justify a comprehensive study. The clinical aspect, pathological physiology, as well as the biological problems

which they impose establish in a way a relationship with chemical nephritis. The authors divide the clinical phases of *transfusional nephritis* into 4 periods: (a) The period of alarm, with subjective symptoms that occur before transfusion has been completed. In such cases renal complications rarely develop. (b) Anuria or oliguria, lasting several days. (c) An inconstant hydric crisis, during which large masses of water are occasionally eliminated by the kidney. (d) The terminal period, during which genuine uremia sets in, sometimes causing death. These authors point out that the *treatment* is symptomatic. They advise **hypertonic salt solution** to be given intravenously. Other suggestions are **decapsulation** to overcome anuria and **high spinal anesthesia**, based on the experimental finding that total denervation of the kidney prevents the disturbances of diuresis by the injection of hemolyzed blood.

Two cases presenting the picture of *uremia after blood transfusion* are reported by O. C. Hansen-Pruss and B. N. Miller (South. M. J. 29:1033 (Oct.) 1936). In one case it is suggested that the transfusion materialized a pre-existing subclinical chronic glomerulonephritis and in the other the kidney tubules probably had been damaged by infection with the *B. typhosus*.

In contrast to this opinion, P. Tassovatz and C. Jung report that *acute grave nephritis* may be treated by **transfusion of blood**. They cite a case in which they believe that **venesection** followed by transfusion was very helpful. They conclude that the various cases they cite show that transfusion of blood preceded by venesection is an excellent treatment for acute nephritis. A large venesection can be made and thus great quantities of toxic substances are removed from the blood. The transfusion has an anti-infectious action

which they claim reduces the inflammation of the kidney, and that transfusion has a tonic effect upon the cardiovascular apparatus.

**Prognosis.**—The prognosis of acute nephritis is dependent not so much on the degree of renal failure as on disturbance of the cardiac function. With this in mind, A. Tur (Klin. Med. 13: 1372 (Sept.) 1935) made a report of his electrocardiographic studies in acute diffuse glomerulonephritis. He states that the pulse is usually slow and regular. Abnormal hearts were found in all but 18 of 119 cases. Half of all cases with acute nephritis possessed an enlargement of the left heart and 15 per cent. of the right heart. According to Bettinardi, then, it must be assumed that changes in the heart muscle take place during acute nephritis. The nature of the changes is in question and only histological studies, which are lacking, can provide an answer. In his article he emphasizes the abnormalities found in the ventricular complexes and other disturbances of conductivity. In the management of the case of acute nephritis the patient's convalescence and his ability to resume work should not be evaluated without the careful study of the heart.

**Treatment.**—In the treatment of acute nephritis the fact must be borne in mind that there is more than merely renal inflammation to deal with, for acute nephritis is a disease not only of the kidney, but of the entire body. It must be remembered that acute nephritis is a sequel of acute bacterial infection and that the patient's energies have been sapped before nephritis commenced. With this in mind the following articles which have appeared this year are of value.

H. Evans (Brit. M. J. 2:400 (Aug. 22) 1936) emphasizes the fact that tardiness in the treatment of acute nephritis may result in the onset of the

chronic phase. In all cases of acute nephritis **warmth and rest in bed** for at least 4 to 6 weeks are necessary. Daily records of blood-pressure, urine volume, and weight are helpful guides in treatment. The **diet** should be restricted, as completely as possible and **fluids** should be **limited** to 1 pint of orange juice in 24 hours. If the blood-pressure does not fall within the first week, **venesection** should be done. When the blood-pressure has gone down the diet may be increased, but should be salt-free, and fluids should not be increased as long as there are any traces of edema. **Surgical removal of septic foci** is advisable, usually after the serious signs of nephritis have subsided. *Secondary anemia* often occurs and should be treated with iron. If there is *heart failure*, it should be promptly treated by **venesection** and the administration of **morphine** and **strophanthin**. When *cerebral complications* occur **venesection** and **lumbar puncture** are valuable aids in improving cerebral circulation. Oliguria and anuria are grave signs if spontaneous diuresis does not occur. Large amounts of fluids will occasionally bring on diuresis but the response to this is disappointing.

J. L. Miller (Texas State J. Med. 31: 638 (Feb.) 1936) stresses the point that the treatment of acute Bright's disease should always be directed at the patient as a whole and not just at the kidney. **Rest in bed** and a simple general **diet**, high in sweets and low in salt, should be enforced. Diuretics are of little value, but **potassium nitrate** is not harmful. It is safer to postpone operative measures until the acute kidney trouble has subsided. *Anemia* is best combatted by **iron**. **Normal salt solution** administered subcutaneously will relieve *vomiting*, but if *acidosis* is present **sodium bicarbonate** should be used and salt withheld.

Advances have been made recently in the treatment of acute nephritis and *B. coli* infections of the urinary tract. T. I. Bennett (Practitioner 135: 433 (Oct.) 1935) discusses these in his report. Acute focal nephritis nearly always clears up completely, but the prognosis in the diffuse variety is more serious. **Rest**, almost starvation **diet**, and **fluid restriction** are necessary in treatment. A diet composed mainly of fruit has been found particularly successful by the author. Fat and protein are to be avoided. If the *urine* is highly *acid*, **alkali-producing drugs** are indicated. The author recommends the **removal of foci of infection**.

An analysis of the value of **decapsulation** is given by A. von Noszkay who studied 12 cases of medical and surgical nephritis. He concludes that the effect of decapsulation may be attributed to the following factors: (a) removal of the capsular tension; (b) the sympathectomy action of the capsular resection and the relief of the angiospasm, with a resulting increase of diuresis and cessation of the kidney pains; (c) drainage of the intraparenchymal spaces. He states that bilateral hematogenic non-suppurative nephritis is basically a medical condition, but that there are mixed forms in which medical treatment is greatly helped by decapsulation. When *acute glomerulonephritis* fails to cure, or progresses under medical treatment, bilateral decapsulation, performed as soon as possible, is to be recommended in order to prevent the condition from becoming chronic. In chronic glomerulonephritis long-continued improvement cannot be expected from decapsulation, but oliguria or anuria may be relieved for a time.

To test the efficacy of **x-ray** therapy of nephritis, G. Bettinardi subjected rats to irradiations proportionately higher than those clinically employed but with-

out attaining the erythematous dosage. In a general way there was no anatomic-histologic injury to the kidneys. However, massive single erythematous dosage did injure the epithelium of the renal tubules. This method of dorsolumbar radiotherapy was carried out clinically in 13 cases of acute, subacute, and chronic nephritis. In 8 cases of acute and diffuse glomerulonephritis, with marked hematuria and oliguria, early treatment with 2, 3 or 4 applications every day or every second day brought about a rapid improvement. In 4 cases of diffuse subacute nephritis with hematuria and oliguria, treated after the fiftieth day of the disease, there was only a temporary improvement. This mode of treatment was ineffectual in a case of fully-established chronic nephritis. When applied in the early stages of the disease, the author believes that x-ray therapy acts favorably in albuminuria, on the general state, on diuresis, hematuria and that it shortens the course of the disease.

**CHRONIC NEPHRITIS.**—Often patients with chronic glomerulonephritis are studied for a short time only and during one period of the disease, usually the advanced stage, when there is evidence of a well-developed renal insufficiency. A more continuous study of a patient over a long period of time usually furnishes some information about the course of the disorder that it would be impossible to gather in shorter periods of observation.

The protean character of the *signs* and *symptoms* of *terminal hemorrhagic nephritis* are outlined by I. H. Page (Ann. Int. Med. 9:1419 (Apr.) 1936). The following points are especially well exemplified in the case he discusses: (a) An insidious onset means a fatal outcome. (b) The terminal stage may last for months. (c) Poor nutrition con-

tributes to discomfort and ill health; therefore, sufficient protein should be given. (d) Salt restriction may relieve edema, even though plasma proteins do not rise above the critical level. If polyuria does not occur, salt restriction may be extreme without producing hypochloremia. (e) Even when hemoglobin is not greatly reduced, death may occur in uremia. Iron will not help the condition. (f) Arterial blood-pressure may alternate between a high level and normal. (g) Eyeground changes may not be present until weeks or days before death. (h) Oliguria may last as long as 18 days without producing marked symptoms. (i) Increased cells may be found in the pituitary gland.

H. Kahler states that there is not a single pathognomonic symptom which is characteristic for any one of the various forms of nephritis. A *differential diagnosis*, therefore, must rest upon the consideration of the entire clinical picture together with the history and evolution of the present disease. Albuminuria alone is almost without significance in differential diagnosis. A moderate degree may persist for a long period of time without indicating that a severe progressive disease of the kidney is present. Similarly, the presence of blood and casts in the urine has to be interpreted in the light of other findings. The relationship existing between the 24-hour output of urine and its specific gravity is always of great importance. If the output is scanty and the specific gravity varies always from 1.011 to 1.013, contracted kidneys are almost certainly being dealt with. If by withholding water the specific gravity can be brought up to 1.025 or more, this fact speaks strongly against the existence of any serious kidney incompetency. An elevation of the blood-pressure does not necessarily prove the

existence of kidney insufficiency nor is it a uniform finding in kidney disease.

After the acute stage has passed, **infectious foci** should be **removed**; if bacteria can be discovered in such foci, it is unconditionally advisable to have an **autogenous vaccine** prepared and to treat the nephritis by subcutaneous injections of this vaccine.

As mentioned by H. Gibbons, the diagnosis and treatment of Bright's disease depends in part on the understanding the physician has of the renal lesion with which he is dealing. A knowledge of the rate at which formed elements are passed in the urine greatly increases the value of urinalysis. The author describes a new rapid method in which the principal difference from the Addis method seems to be a means of comparing the turbidity of urine containing protein with a standard solution. With average office facilities a constantly uniform picture can be obtained (in conjunction with other clinical evidence) of every pathologic state of the kidneys.

According to T. S. Evans, there are no methods by which renal impairment can be diagnosed and the course followed. The renal margin of safety may be small and some injury will bring about a breakdown. A case is presented of a woman who had 3 such breakdowns brought on by self-imposed lack of food and fluid. From the first two she recovered for periods of 1 and then of 5 years. During the periods of remission the glomerulonephritis was progressing even though there were no symptoms.

In an interesting article B. Misske and W. Otto (*Folia haemat.* 55:182, 1936) discuss the *pallor* of patients with *chronic glomerulonephritis*. They say that the paleness may be due to spasms of the blood vessels of the skin, deposits of pigment, or anemia. They found anemia in 44 per cent. of the cases of chronic glomerulonephritis without

marked disturbances of renal function. The average hemoglobin content was 70 per cent., while the average number of red corpuscles was 3,730,000. The same relations were found between the anemia and the nonprotein nitrogen. Moderate leukocytosis was observed in 54 per cent. of all cases.

As in acute nephritis, many patients with *chronic nephritis* die of nonrenal causes. Of 66 patients with chronic nephritis studied by A. B. Richter and J. P. O'Hare (*New England J. Med.* 214:824 (Apr. 23) 1936) chronic hypertension was present in all but 5 cases. Angina pectoris and coronary thrombosis were infrequent and pericarditis was the most common cardiac disorder. The heart was enlarged in all cases. Gallop rhythm was found in the late stage of one-third of the cases. In 43 per cent. there were various kinds of murmurs, and congestive heart failure developed in 23 per cent. a few months before death. Pericarditis was present in 48 per cent. of the cases and death occurred at an average of 7 days after the pericardial rub was heard. The electrocardiogram showed little abnormality before the onset of pericarditis. One or both coronary arteries were thickened in 14 cases. The histological changes in the myocardium were relatively unimportant.

Acute attacks of *hyperazotemia with grave uremia associated with hypochloremia* are described by H. Chabanier, C. Lobo-Onell, P. Lieutaud and E. Lelu. These authors cite a case of excessive retention of nonprotein nitrogen in the blood. They summarize their findings by stating that apparently a marked hypochloremia of the plasma of the blood corpuscles was present in the patient. The administration of **chloride** produced surprisingly good results on the toxic phenomena and the secretory disturbances of the kidney. Administra-

tion of chlorides may fail to produce the expected results in postoperative conditions as well as in exacerbations of chronic nephritis. In all cases with acute attacks of azotemia, lesions of the tubular epithelium were found. Such cases as those of toxic origin observed in nephritis after mercurial poisoning are cited. They explain that the syndrome of hyperazotemia developed in their cases when the salt-free diet, which caused a large loss of blood chlorides was observed, but there are other causes for the hypochloremia. Chlorides exert a neutralizing effect on the blood stream of these patients. If this neutralizing action is insufficient, a toxic syndrome appears unless a sufficient amount of **sodium chloride** is administered to break the vicious circle.

We are reminded that in the majority of patients with *chronic nephritis* the 4 classical syndromes described by Widal are found, *viz.*, *albuminuria*, *hypertension*, *chloruremia*, and *azotemia*. R. Benard, M. Poumailloux and A. Negreanu (Bull. et Mem. Soc. Méd. d. Hôp. de Paris 52:47 (Jan. 27) 1936) cite a case of chronic nephritis with the azotemic but without the chloruremic or hypertension syndromes. They summarize their findings by stating that the azotemic syndrome was followed by a typical uremic coma. Albuminuria was moderate and only an increase of weight suggested a retention of chlorides. In view of the renal syndrome an extrarenal cause for the azotemia cannot be assumed. A coexistence of hypertension and renal lesions cannot be denied, but a statement that renal sclerosis is always followed by hypertension is not correct.

High *blood urea nitrogen* may not always be due to chronic nephritis. Recent literature includes reports of high blood urea nitrogen not associated with chronic renal failure. In an article by M. G. Wohl and R. W. Brust (J. Lab.

and Clin. Med. 20:1170 (Aug.) 1935) a list of nonrenal conditions that may be responsible for elevated nonprotein nitrogen is given: (a) vomiting, as in gastric cancer, pyloric spasm, toxemia of pregnancy, gastric tetany, acute intestinal obstruction, or acute peritonitis; (b) repeated gastric lavage; (c) diarrhea; (d) cerebral hemorrhage; (e) reflex anuria; (f) diabetes mellitus; (g) extensive burns; (h) pancreatic necrosis; (i) infectious diseases. The differentiation between chronic glomerulonephritis and nonrenal azotemia is pointed out. If the nonprotein nitrogen and urea nitrogen values are high, blood chloride values are apt to be diminished and the carbon dioxide combining power of the blood plasma increased. The nonprotein nitrogen content of the blood is the result of 3 factors, *i. e.*, the rate of protein breakdown in the body, the concentration powers of the kidneys, and the amount of water secreted. With a great protein destruction, as in emphysema or lobar pneumonia, the nonprotein nitrogen may rise when the kidneys are normal, especially if the water excretion and intake are slight.

That *chronic azotemic nephritis* may occur without hypertension is further emphasized by M. Labbé (Rev. gén. de clin. et de thérap. 49:801 (Dec. 7) 1935). He says that renal acidosis may be latent in spite of a very low alkaline reserve or may be manifested by Kussmaul's respiration. In diabetes, the ketone bodies are found in the urine a long time before the appearance of coma, but this is not the case in renal disease. Patients with uremia have more phosphoric acid and phosphates in the blood than normal individuals, but it is not true that the urine contains less acid in Bright's disease. It has been supposed that the body retains organic acid in these cases, but examinations have not shown the slightest change.

In Labbé's case the permeability of the kidney to water was very defective, but the kidneys were permeable to sugar, which was eliminated in small quantities. He could find no reason either clinically or anatomically why the patient should not have had hypertension. From the contradictions of these biologic investigations, it can be seen how difficult it is to understand the various functions of the kidney in chronic nephritis.

*Renal Function Tests.*—The number of articles dealing with new renal function tests and modifications of old ones is so large that it is convincing that there is as yet no ideal method of measuring kidney function. After using many tests over a period of years, the practitioner is inclined to rely on the simple methods, and the simpler the better. Furthermore, it must be borne in mind that the whole story of loss of reserve power of the kidney is not told by the laboratory functional tests alone; information obtained from numerous renal function tests must be blended with certain clinical features and the capacity of the kidney assessed only after a long period of observation.

It has been recognized for years that the most important renal function test is the determination of the *specific gravity* of the urine. The inability of the kidney to secrete concentrated urine is an early sign of renal failure. Many modifications of this simple test have been used. Last year R. H. Freyberg (J. A. M. A. 105:1575 (Nov. 16) 1935) stated that the degree of albuminuria and hypertension is of little importance compared to functional capacity of the kidney as an accurate index of the seriousness and prognosis of Bright's disease. The methods of determining renal sufficiency are based on the following principles: (a) the ability of the kidney to concentrate the urine; (b) the ability of the kidney to secrete introduced substances

as dyes; (c) the effectiveness of the kidney in secreting the waste products of metabolism as estimated by the clearance tests. The most sensitive test of all is the *concentration test*. Low specific gravity indicates renal impairment. He believes that the phenolsulphonphthalein test is not a sensitive one, but that when the normal amount of dye is excreted after injection, it is safe to believe that no very great renal damage exists. On the other hand, when a low excretion of dye is found there may be severe renal failure; yet extrarenal factors may interfere to such an extent that the low excretion is not an actual estimation of the functional capacity. In this article the author gives a fairly detailed account of these tests and concludes that the most accurate and complete information concerning renal function is obtained from the use of the *concentration* and the *urea clearance tests*.

Since the introduction of the practical urea clearance test by Van Slyke and his associates a number of years ago, many studies and certain improvements have been made on this procedure.

The use of a micromethod for the determination of urea in the blood and an automatic urine collector have made the measurements of *urea clearance* in infants more effective. Such a method of study has been described by L. E. Farr (J. Clin. Investigation 14:911 (Nov.) 1935) who makes the test on as little as 0.25 c.c. of blood.

E. M. Landis, K. A. Elsom, P. A. Bott and E. Shields (Ibid. 14:525 (Sept.) 1935) draw attention to the relation between *sodium chloride* and *urea clearance* in cases of renal insufficiency. Average 12- and 24-hour urea clearances were used to study the effects of sodium chloride restriction and administration on renal function in 3 patients with different degrees of insufficiency. When diet and fluid intake were constant,

restricted intake of sodium chloride brought a slight elevation in plasma urea nitrogen and a slightly diminished urea clearance. Sodium chloride administration brought a lowering of the plasma, urea nitrogen, and a higher average urea clearance. In a patient with advanced renal insufficiency, the plasma urea nitrogen dropped from 154 to 26 mg. per 100 c.c. during sodium chloride administration. Restriction produced hypochloremia and temporary retention of urea, creatinine, and phosphates, which was relieved by renewed salt intake. The authors suggest that this method of study may aid in determining the factors responsible for the association of hypochloremia and azotemia.

In an excellent resumé L. Leiter points out the *limitations* and *indications* of renal function tests in clinical medicine. He emphasizes the point that no renal function test is a true measuring stick in diagnosis and prognosis, for extra-renal factors, such as heart disease and anemia, at times play an important part. The distinction between focal and diffuse glomerular nephritis has become of doubtful value, since impaired renal function has been demonstrated by the urea clearance test in the so-called focal cases. Of the commonly used renal function tests in clinical medicine, Volhard dilution and concentration test, the phenolsulphonphthalein test, and urea clearance test, he considers the *urea clearance test* the most reliable and most useful.

The same view is presented by E. Hinden, who points out that the *urea clearance test* is of most value in cases of moderate impairment and that most other tests show no difference in these circumstances. From his experience he concludes that the test is an accurate index of the clinical condition of the patient. Other tests fail to give an indication of defective renal function as early as the urea clearance test.

*Blood Chemistry.*—A. Lemierre is of the opinion that determination of the *blood urea* is the only method of discovering renal involvement in the eruptive stage of scarlet fever. If the kidney involvement is intense, there may be oliguria and uremia. In early uremia, renal hypertension is always absent; if albuminuria exists, it is late and transitory. Edema appears only under exceptional circumstances. These characteristics are a contrast to the nephritides of convalescence, in which albumin, hematuria, edema, and arterial hypertension are present and are apparently unrelated to the level of the blood urea.

*Quantitative indican determinations* have been made on the blood and the urine in an effort to determine the degree of renal insufficiency. S. H. Polayes and E. A. Eckert found that increases in blood indican values were accompanied by increases in blood nonprotein nitrogen content. At times they found the blood indican normal in cases in which the nonprotein nitrogen of the blood was increased and in which postmortem examination showed evidence of advanced renal disease. Increases in the blood indican were found to be only temporary in instances of urinary obstruction. Removal of the cause of obstruction was followed by the return of the blood indican values to normal.

N. O. Irdelp, M. Guchan and M. Kazim state that the determination of the *xanthroproteic reaction* in cases of nephritis can give exact indications, especially from the point of view of renal insufficiency. It rounds out the findings furnished by the blood urea content. The technic is simple.

The serum plasma or blood is de-albuminized with an equal quantity of 20 per cent. trichloroacetic acid. To 2 c.c. of this de-albuminized filtrate, placed in a test tube, 0.5 c.c. of concentrated nitric acid is added and the mixture held over a flame for about half a minute without being allowed to boil. After cooling,



1.5 c.c. of a 33 per cent. solution of sodium hydrate is added and the total volume brought up to 4 c.c. by adding distilled water. After 10 minutes the yellow color of the mixture is compared in a colorimeter containing potassium chromate 0.03874 per cent. The intensity of the color of the serum to which nitric acid and sodium nitrate has been added varies according to the volatile bodies set free after hydrolysis. The value of the xanthoproteic reaction in normal subjects varies from about 15 to 35 in the colorimeter scale; it may run up to 100 in cases of uremia with lesser values in other kidney lesions.

An article dealing with increased *non-protein nitrogen* of the blood subsequent to loss of fluids after vomiting and diarrhea is given by M. Rachmilewitz. The increase of urea nitrogen in the blood is generally considered a serious sign of kidney insufficiency and the result of incomplete excretion. The occasional occurrence of the retention of urea in nonrenal diseases such as diarrhea and decompensated heart cases has been considered a sign of kidney damage. Following the administration of chlorides and glucose, the toxic symptoms disappear and urea in the blood diminishes. Owing to a sudden great loss of fluids and salts, a profound disturbance in mineral balance of the body occurs, with consequent disturbance of general metabolism.

**Treatment.**—A resumé of the modern view of nephritis and its treatment is given by F. A. Roper (Clin. J. 64:351 (Sept.) 1936) who says that there are 3 groups of "medical" kidneys, *i. e.*, degenerative, inflammatory, and vascular or arteriosclerotic. The *arteriosclerotic group* is due to atrophy caused by diminished blood supply in essential hypertension. The treatment, therefore, is directed at circulation. The main class of the *inflammatory group* is the diffuse nephritis occurring as a sequel to some bacterial infection and is a result of toxins attacking every nephron. Diminished blood supply because of vascular

blockage leads to lowered urinary output and greater permeability. There may be a "silent period" between the acute and chronic phases, or the transition may be a gradual merging of the acute into chronicity. In treating inflammatory nephritis **nitrogenous foods** should be **cut down** to avoid the retention of their waste products. **Water restriction** is advisable if diuresis is satisfactory. In the *acute* form of *nephritis* diuretics should not be used. Nephrosis is the purely degenerative process. Albuminuria and consequent edema are the only signs. *Renal edema* is treated by **diet high in protein, diuretics, urea and salyrgan**, and in obstinate cases **drainage by incision or Southy tubes**. In *chronic nephritis* the edema may be mixed in origin and full investigation is necessary. The theory that a disorder in chloride metabolism causes edema is no longer tenable. However, salt is retained in the tissues, so a **salt-free diet** should be imposed in cases of edema. Oliguria should not be treated by increased fluid.

The outstanding points in the treatment of *chronic nephritis* and *uremia* are well described by R. Platt (Brit. M. J. 2:437 (Aug. 29) 1936). According to this writer the treatment can be aimed only at slowing down its course and relieving the symptoms. The patient should not be restricted too much. Overexertion, infections, and temperature changes should be avoided and septic foci should be dealt with early in the disease. No medicinal treatment is of value, but the bowels should be kept active and *anemia* combatted with **iron**. Protein in the **diet** should be reduced to the necessary minimum. If no edema is present, fluids and salt need not be restricted. Fat should be minimized especially in the presence of hypertension. If *heart failure* complicates the disease, **rest in bed, fluid restriction**

and some **diuretic** should be employed. Digitalis is of little use unless auricular fibrillation is present. **Morphine** will relieve nocturnal *dyspnea*. *Cerebral attacks* occur when the blood-pressure is very high and is relieved by **magnesium sulphate**, **leeches** applied to the temple, **venesection**, and **lumbar puncture**. **Phenobarbital** may be used to prevent future attacks. When true *uremia* is recognized the **diet** should be reduced to fruit, glucose, and water, the **fluid intake** being liberal. **Glucose** intravenously and by rectum should be administered. *Vomiting* may be controlled with **sodium luminal** and "*renal asthma*," due to acidosis, is relieved by **sodium bicarbonate**.

Because of the unique position of blood protein in the pathogenesis of renal edema, the problem of protein in the **diet** in the treatment of patients with nephritis has been extensively discussed. C. S. D. Don (Ibid. 1:985 (May 16) 1936) states that in acute and chronic nephritis without edema, ordinary amounts of protein do no damage to the kidney, but protein gives work to the kidneys, so if they are damaged it is safer to restrict protein to some extent. Such a restriction must not be carried to the extreme limit formerly advocated. Don recommends 0.6 gm. (10 grains) of protein per kilogram ( $2\frac{1}{5}$  lbs.) of body weight and states that in the nephritic type a high protein diet is indicated.

The influence of protein in the **diet** on plasma protein of patients with the chronic stage of *chronic glomerular nephritis* is discussed by E. H. Keutmann and S. H. Bassett. Three patients with chronic glomerular nephritis in the nephrotic stage were studied. The intake of protein was greatly increased and there was a marked deposit of nitrogen in their bodies. Yet there was no increase in the amount of circulating protein

in two cases. In the third there was considerable improvement. Albuminuria increased following excessive intake of protein. It may be concluded that the problem of increasing the plasma protein must be met not by increasing greatly the protein in the diet, but by decreasing the leaking away of albumin in the urine through a decrease in the permeability of the capillary membranes of the glomeruli. There is apparently no lack of ability in the patient with nephrosis to synthesize new protein.

The high protein **diet** is considered by J. F. Hart (M. Rec. 141:574 (June 19) 1935) not to be harmful. He believes that such diets are beneficial in all kinds of nephritis except in those cases where the products of nitrogen metabolism are retained in the blood stream. The minimum amount of protein, that is 0.6 gm. (10 grains) per kilogram ( $2\frac{1}{5}$  lbs.) of body weight, is required in those cases where nitrogen is retained.

*Diuresis*.—The subject of edema diuretics, and diuresis is very clearly and completely discussed by H. A. Christian (Proc. Inst. Med. Chicago 11:149 (Nov. 15) 1936). Justice can hardly be done to this splendid article in a short resume, for it is a summary of present knowledge of the subject. He points out that the treatment for renal edema is just the same whether dealing with nephrosis, nephritis or the edematous type of acute nephritis. To date there are no means for ending an excessive albuminuria, and the hope of accomplishing this seems to lie in the possibility of this edema turning out to be the result of some vitamin or other type of food deficiency. To replace the lost plasma protein, high protein diet and blood transfusions are used, but rarely is there any striking increase in the plasma protein. However, it is wise to place *edematous nephritics* on a high protein **diet** as a general rule of therapy.

Diuretic drugs are necessary to reduce edema. Xanthine diuretics, as a rule, are of little use, but **mercurial diuretics** are usually effective and, as a rule, cause no renal irritation. **Urea** in large doses is an efficient diuretic if it can be tolerated by the patient. The author finds that intravenous injections of 400 c.c. ( $\frac{4}{5}$  pint) of 15 per cent. **gum acacia** is often an excellent diuretic, but every care must be taken to avoid an impure substance, as it may cause serious reactions.

H. M. Hand has investigated the question of serum concentration in different types of *edema*. If serum proteins have fallen below the critical level of 5.5 grams, a potential edematous state exists. As to the site of the formation of plasma proteins, very little evidence appears. Edema may be found in a variety of clinical conditions and may be due to (1) insufficient intake of protein, (2) excessive loss of protein, (3) protein destruction due to chronic infections or cachetic states, (4) inadequate formation of decreased assimilation of proteins. He concludes that the low levels of serum proteins with resulting *edema* are best *prevented* by **adequate intake of protein**. The edema is most successfully *treated* by **high protein diet, restriction of sodium chloride, diuretics, blood transfusions**, and intravenous administration of **acacia**.

J. B. Rennie states that whether the fall in serum proteins be regarded as the direct cause of renal edema or merely as one of the associated phenomena of nephritis, their estimation is of undoubted value both as an aid to prognosis and a guide to treatment. If *serum proteins* are found to be *normal* or but little reduced, treatment by **fluid diet, a saline aperient** and the **hot-air cage** yields good results. If *serum proteins* are *below the critical level*, gross hematuria, azotemia and elevation of blood-

pressure being absent, the case is one of the nephrotic type; the diet should contain **adequate protein** and must be **salt-free**. If dietetic measures alone fail, then **ammonium chloride** or **salyrgan** may be used in addition.

**ESSENTIAL HYPERTENSION (THE NEPHROSCLEROSES).**—The view is expressed by many that there are two types of essential hypertension, designated the "red" and the "pale" types by the Germans. In this country the terms benign and malignant are used to express the same disorders. *Malignant nephrosclerosis* from the clinical and pathological standpoint should not be looked upon as merely a progression of benign nephrosclerosis, but rather as a distinct disease. It may occur alone or as a terminal stage of the benign disease. This is the viewpoint expressed by H. E. MacMahon and J. H. Pratt (Am. J. M. Sc. 189:221 (Feb.) 1935). Although their very careful clinical and pathological study warrants their drawing this conclusion, there are many who will disagree with them. The most widespread idea of the relationship between the benign and malignant types is that both are stages of one arteriosclerotic process, differing from one another not in type but in degree.

A review of the year's literature on the subject of Bright's disease cannot help but show that the most outstanding work has been done in the field of the treatment of hypertension. Interest in this field of work has been stimulated by surgeons who have attempted to control hypertension by operations on the autonomic nervous system. They assume that hypertension is caused by peripheral vasoconstriction and that by cutting the controlling sympathetic fibers the peripheral constriction is overcome.

Before taking up a review of the surgeons' articles the REVIEWER shall briefly outline what is considered the year's most outstanding contribution to the literature on the nature of arterial hypertension. This is the paper of M. Prinzmetal and C. Wilson (J. Clin. Investigation 15:63 (Jan.) 1936). By studies on the blood flow in the arms under various conditions, using the arm plethysmograph, they were able to draw certain conclusions: (1) The increased vascular resistance in different types of hypertension is not confined to the splanchnic area, but is generalized throughout the nervous system. (2) Increased fiber resistance is due to hypertonus and not to organic changes in the vessel wall. (3) This hypertonus must be regarded as intrinsic spasms of the blood vessels themselves and is dependent on vasoconstrictive action. (4) All types of hypertension, the benign, the malignant, and the renal, are produced by the same type of mechanism. (5) In the types of hypertension studied it appears that normal vasoconstrictor action is superimposed on an intrinsic vascular hypertonus leading to acute elevation of blood-pressure. (6) Surgical procedures aiming at the relief of high blood-pressure by sympathectomy do not abolish vascular hypertonus which is responsible for the high blood-pressure. They merely remove the superimposed vasoconstriction.

In support of the theory that the rise in blood-pressure is caused by a widespread vasoconstrictor action, E. A. Hines, Jr. and G. E. Brown (Am. Heart J. 11:1 (Jan.) 1936) describe what is known as the cold pressor action. This is a test to measure generalized vasomotor tonus and ice water is used as a stimulus. The patient is allowed to rest in a quiet room for 20 to 60 minutes. The cuff sphygmomanometer is placed on one arm and the opposite is immersed

in ice water to a point just above the wrist. Pressure readings are taken at the end of 30 and 60 seconds. The maximum reading obtained while the hand is in ice water is taken as the index of response. The maximal response occurs within 30 seconds and in normal people the blood-pressure returns to the basal level within 2 minutes. In the hypertensive there is a delay. With this test it is possible to select patients who have a tendency to develop hypertension.

The mechanism of peripheral resistance and persistent high blood-pressure was studied by G. W. Pickering (Clin. Sc. 2:209 (May) 1936). He found that under similar conditions the rate of blood flow through the forearm is the same in subjects with essential hypertension, malignant hypertension, and chronic nephritis with hypertension, as in subjects with normal blood-pressure. After periods of circulatory arrest, the rate of blood flow increases to the same extent in the normal and hypertensive patient. In both normal and hypertensive subjects the rate of blood flow through the cutaneous vessels in the hands declines after inhibiting vasoconstrictor nerve impulses as age advances, due to arteriosclerotic changes in the hand vessels. The author concludes that in essential hypertension and chronic nephritis the agent narrowing the vessels is not nervous.

The importance of the *blood cholesterol* as an etiological and prognostic factor in essential hypertension has been emphasized repeatedly in the past. This year another study was made of the plasma lipids in essential hypertension by I. H. Page, E. Kirk and D. D. Van Slyke (J. Clin. Investigation 15:109 (Jan.) 1936). They chose 16 patients with idiopathic hypertension whose hemoglobin and urea clearance were still within normal limits. They were in good condition and free from complications

which might affect blood lipids. There was no tendency toward abnormality in the total plasma lipid contents, combined or free cholesterol, or any of the lipid fractions determined. Hypercholesterolemia may be a predisposing factor to arteriosclerosis. In the two advanced cases of malignant sclerosis, lipid values fell above or in the upper normal ranges.

In the past, iodine has occupied a place in the therapeutics of hypertension and arteriosclerosis. A recent article by F. Domrau (M. Rec. 144:373 (Oct. 21) 1936) shows the effect of Burnham's soluble **iodine** in the treatment of 20 cases of hypertensive arteriosclerosis. Symptomatic relief was obtained in 90 per cent. of the cases and complete relief in 65 per cent. Improvement, he says, was not paralleled by reduction in blood-pressure. The chief criterion for gauging the effectiveness of the treatment lay in the patient's symptomatic improvement rather than in any tangible changes in blood-pressure.

Another old therapeutic measure in the treatment of hypertension has been revived recently by M. H. Barker (J. A. M. A. 106:762 (Mar. 7) 1936). He gave **sodium** or **potassium thiocyanate** to 45 patients with hypertension and followed the cyanate concentration of the blood. The reduction of blood-pressure and relief of symptoms obtained in 35 cases corresponded to the level of the blood cyanates. The optimum therapeutic level seems to range from 8 to 12 mg. per 100 c.c., and toxicity appears at from 15 to 30 mg. Individual tolerance varies widely. The administration of thiocyanates is dangerous unless controlled by close observation and blood cyanate determinations.

At times, patients with severe chronic hypertension suffer from the effects of increased *intracranial pressure* and several methods have been reported for its relief. This year F. D. Murphy,

R. A. Hershberg and A. M. Katz (Am. J. M. Sc. 192:510 (Oct.) 1936) have given a report on the effect of **intravenous injections of sucrose solution** on the cerebrospinal pressure, blood-pressure and clinical course in chronic hypertension. In brief, favorable results with the relief of headache, nausea, vomiting, dizziness, convulsions, and other symptoms of increased intracranial pressure were achieved by giving intravenously 200 c.c. (6 $\frac{2}{3}$  ounces) or more of 50 per cent. sucrose solution. A prompt and profuse diuresis followed such injections. In the series of cases reported no unfavorable results were noted; yet in the paper it is emphasized that such a hypertonic solution must be administered slowly and with great care. Clinically, the patients were improved.

The *efficacy of medical treatment* of essential hypertension is brought out by R. S. Palmer (New England J. Med. 215:569 (Sept. 24) 1936). The 169 patients studied by him were classified according to age and the degree of hypertension. In the mild form of the disease 90 per cent. of all ages either have no symptoms or are easily relieved. In the moderate form there is a 50 per cent. chance of a fall in blood-pressure in all age groups and 75 per cent. can be much relieved. In a patient under 46 years of age radical therapeutic measures must be considered, since in this age the malignant form occurs most commonly, especially among females. Medical treatment in this condition is of no value and any surgical help giving symptomatic relief is most welcome. In the group over 46 a fall in blood-pressure is possible in one-third of the cases and symptomatic relief in 46 per cent. The vascular changes are irreversible and surgery will do no good.

The **surgical treatment** of essential hypertension is outlined by G. J. Heuer (Ann. Surg. 104:771 (Oct.) 1936),

who selected 18 patients with various forms of hypertension for anterior nerve section. The flexibility of the vascular tree, blood-pressure, eye ground changes, basal metabolism, renal efficiency, and heart changes were carefully studied before and after operation. The outcome in 3 cases was bad. Of those remaining, subjective improvement was very marked in 3, marked in 8, and moderate in 2 cases. Lowering of the blood-pressure and improvement of the eye ground condition has varied. In all but two cases there was a fall in blood-pressure which has persisted for 2 years. The author concludes that the operation is beneficial for patients with benign hypertension and young patients with signs of the hypertensive diencephalic syndrome. He has also done **splanchnic nerve resection combined with removal of the lower thoracic sympathetic ganglia** in 9 cases with disappointing results. The relief from both subjective and objective signs was minimal.

M. M. Peet (Univ. Hosp. Bull. Ann Arbor 1:17 (June) 1935) performs a different operation for the control of hypertension. He does a **bilateral resection of the roots of the splanchnic nerves with resection of the lower sympathetic chain**. He believes that in this way the renal vasoconstriction is removed and interrupts the pathway of stimulation of the adrenal gland and prevents a large vascular area from undergoing vasoconstriction and stimulation.

Investigators and clinicians who know most about the subject of hypertension believe it is too early to make any sweeping conclusions regarding the value of these surgical measures in the treatment of hypertension. Whether or not they prove eventually to be of value, they at least have augmented knowledge of the processes involved in the produc-

tion of hypertension. Surgeons have stimulated others to think more carefully and clearly about the possibilities of therapeutic agents in chronic hypertension.

The surgical treatment of essential hypertension is discussed by G. Crile (Cleveland Clin. Quart. 3:201, 1936) and a report of the progress of 106 cases is given. The operation consists in **denervation of the adrenal glands and division of the splanchnic nerves**. His impressions from experiences with 25 cases are summarized as follows: (1) During the operation the blood-pressure in malignant hypertension is reduced to normal level. (2) There is but a slight degree of shock. (3) The operation is performed in one seance. (4) Nitrous-oxide oxygen provides ample anesthesia. (5) This operation gives the impression of being a complete procedure. The results have been improvement in the eye grounds and in kidney function as well as in the general well-being of the patient.

**THE NEPHROSES.**—The nephroses and particularly so-called lipid nephrosis are having difficulty in maintaining their identity in modern classifications of Bright's disease. H. Elias (Wien. klin. wchnschr. 48:1177 (Sept. 27) 1935) states that on purely anatomical grounds the medical lesions of the kidney may be divided into 3 principal divisions: (1) degenerative processes which attack principally the epithelial cells and the tubular apparatus; (2) the inflammatory processes; and (3) the sclerotic processes involving primarily the blood vessels of the kidney. To the first category belong the nephroses which are brought about by infectious diseases. Chronic lipid nephrosis is due to some chronic infection, such as syphilis, malaria, chronic rheumatism, or tuberculosis, or to the ingestion of chemical

poison, such as mercury, permanganate or carbon monoxide. The poison may result from an autointoxication, such as in pregnancy, diabetes or goiter. Loss of albumin brings about alteration of osmotic pressure, with resulting edema.

The after-history of 6 cases of *lipoid nephrosis* was studied carefully by R. H. Major (Am. J. M. Sc. 191:43 (Jan.) 1936). They all showed marked edema, normal blood-pressure, absence of cardiac enlargement, heavy albuminuria, high blood cholesterol, low blood proteins, inversion of the albumin-globulin ratio and diminished basal metabolic rate. Two patients died, showing at autopsy evidences of chronic glomerular changes; 3 have apparently recovered; and 1 still shows a trace of albumin. All types of therapy were used, including high protein diets, blood transfusions, intravenous glucose, thyroid extract, parathormone, and various diuretics. **Blood transfusions and intravenous glucose** gave temporary relief. Thyroid extract and parathormone did no good. There seemed to be no bad effects from **novasurol** or **salyrgan**. Gum acacia was given in one case and the next day the patient developed acute nephritis with exitus. A very **high protein diet**, 600 to 800 grams a day, seemed to have remarkable results.

In *lipoid nephrosis* the outstanding features are a heavy albuminuria, edema, and hypercholesterolemia. Treatment is aimed at the edema. The effect of increasing the plasma protein by giving a large quantity of protein in the diet has been seriously questioned. **Acacia** has been used to increase the colloidal osmotic pressure of the blood plasma. M. W. Dick, E. Warweg and M. Andersch (J. A. M. A. 105:654 (Aug. 31) 1935) believe that acacia in the treatment of nephrosis is not only useless but harmful. They advise against its use.

On the other hand, some striking results have been reported. For example hypoproteinemic nephrosis and its treatment with **acacia** has been reported upon by J. H. Barach and D. H. Boyd. Nephrosis, according to these writers, is a disease of metabolic origin. The glomeruli at times show histologic changes. Two cases were treated with acacia in 30 per cent. solution with 4½ per cent. sodium chloride. If the acacia is dark or cloudy it causes reactions. In both cases all therapeutic measures had failed until acacia was given. The results were striking. Diuresis was started and edema disappeared. Both patients were discharged with slight albuminuria as the only remaining symptom.

The REVIEWER'S experience with **acacia** has led him to look upon its use with favor. However, he does not advise using it until other therapeutic aids have been exhausted. In one case particularly, all of the usual methods of treatment were employed but the youthful patient with an extensive aggravating edema grew worse. As a last resort, 400 c.c. of 20 per cent. acacia were injected intravenously. This was repeated 2 days later and marvelous results were obtained. The REVIEWER, therefore, does not agree that acacia is useless in the treatment of nephrotic edema; yet he is in accord with those who advise its use in selected cases.

R. Platt (Brit. M. J. 2:548 (Sept. 12) 1936) has pointed out some features in the treatment of *lipoid nephrosis*. He recommends that the patient be confined to **bed** and carefully guarded against exposure and infection. **Salt and water** should be **restricted** and a high protein, low fat diet given. **Urea** as a diuretic is valuable. If that fails, the **mercurial diuretics** may be resorted to, providing there is no hema-

turia, hypertension, or nitrogen retention. Iron will help combat anemia and **thyroid extract** is often an aid. **Fluid in the pleural and abdominal cavities should be removed**, but Southy tubes are to be avoided unless the patient is in great distress. Some fluid may be removed via the sweat glands if **hot packs** are used. Any **focus of infection** should be **removed** early in the disease. Nephrosis is usually fatal and always serious, but remissions and even complete cures may come about suddenly and spontaneously.

The *relationship of nephrosis to hypothyroidism* has been dealt with by J. A. Baird (M. Bull. Vet. Admin. 11:272 (Jan.) 1935). He reports on a patient who was admitted to the hospital enormously bloated. The only abnormal findings were a heavy albuminuria, a low basal metabolic rate, and anemia. The patient started to improve when transferred from a low to a high protein diet. He was finally put on **thyroid** medication and the anasarca cleared up. Heart disease, glomerular nephritis, parasitic infestation, and nutritional edema were ruled out. It is thought to have been a case of primary nephrosis and the indications are that thyroid unbalance was an important factor.

In an extensive article on the diet in the management of nephrosis, C. J. Barborka points out the following important factors: (1) High protein content, (2) low fluid intake, (3) low salt, (4) low fat content, and (5) high carbohydrate content. The **fluid intake** must be **limited** to an amount that will approximately balance the output of the kidney without the influence of diuretics. Since the blood plasma is low in protein and high in fat, the diet should be low in fat and high in protein. He gives diet tables which are very satisfactory guides in the treatment of the patient.

## TUBERCULOUS NEPHRITIS.

—A summary of the *treatment* of tuberculous nephritis is given by L. Ramond. (1) **Complete rest in bed with windows wide open**, the kidney region being **protected by a wide flannel band**; (2) **lacto-vegetable salt-free diet** at first and as soon as possible a nourishing **mixed diet** compatible with the state of the kidneys; (3) daily administration of 2 Gm. (30 grains) of **calcium chloride**; (4) *abstention from* all antituberculous chemical medication which acts on the kidneys (*creosote, gold salts*). These are contraindicated on account of their effect on the nephritis.

**RENAL RICKETS.**—The subject of renal rickets or, as it is sometimes called, renal infantilism or dwarfism, has received considerable attention in the literature of the past year. D. H. Shelling and D. Remsen report a case and give a brief review of the literature on the subject. They favor restricting the term renal rickets to those cases in which the rickets result from chronic renal disease. They point out that renal rickets is sometimes confused with primary hyperparathyroidism and that there are difficulties in the differentiation. In their case the underlying cause of renal impairment was bilateral hydronephrosis, probably the result of obstruction in the genitourinary tract. They found the presence of increased amounts of parathyroid hormone in the blood and 4 enlarged parathyroids at autopsy. They believed that the secondary parathyroid hyperplasia was due to the phosphate retention and to the demineralization of the skeleton. Renal rickets is due to the necessity of excreting retained phosphate as the insoluble salt of calcium in the bowel, and to the compensatory secretion of increased amounts of parathyroid hormone.



# DISEASES OF METABOLISM

Edited by JOSEPH T. BEARDWOOD, JR., A.B., M.D.

## DIABETES

By FREDERICK M. ALLEN, M.D.

**Pathogenesis.**—HYPOPHYSIS AND PLURIGLANDULAR INFLUENCES.—The most important development of recent years bearing upon the theory and nature of diabetes is the demonstration of the rôle of the *anterior lobe of the hypophysis*. The credit for the primary discovery belongs to Houssay (B. A. Houssay and L. F. Leloir: *Compt. rend. Soci. de biol.* 120:670, 1935; *New England J. Med.* 214:1128 (June 4) 1936), who proved first in toads and later in mammals that this organ exercises a remarkable influence upon the diabetes following total pancreatectomy. Extirpation of the anterior pituitary not only reduces very greatly the glycosuria and hyperglycemia following pancreatectomy, but also extends the life of the experimental animal from a few days or weeks up to several months. Implantation of anterior pituitary tissue in such cases restores the diabetes in full violence. These observations have been confirmed and extended by a number of workers in different parts of the world. One of the most recent is D. Slome (*J. Exp. Biol.* 13:1 (Jan.) 1936), who not only corroborated the extirpation experiments, but added the proof that in toads the color changes of the skin in light or dark environment are due to stimulation of different parts of the hypophysis, and that a corresponding elevation or reduction of the blood sugar occurs with the mere change of illumination. H. M. Evans obtained prolonged or chronic hyperglycemia and glycosuria in consequence of prolonged injections of anterior lobe extract in normal dogs. Hypophysec-

tomy makes rabbits supersensitive to insulin (Corkhill, Marks and White, 1933).

The pluriglandular interest thus aroused has revealed important new relationships. The frequency of diabetes with pituitary disorders, such as acromegaly, has long been known clinically, and it is conceivable that control of the pituitary hyperfunction by surgery or radiation may ameliorate this form of diabetes. The question of an occult pituitary disorder assumes importance in connection with the question of insulin resistance. Reports of diabetic cases which fail to respond with the usual readiness to insulin are published in increasing numbers, and among the possible complicating factors which may possibly account for this peculiarity, an abnormal pituitary function is most frequently suspected. The number of cases treated by resection or more often irradiation of the hypophysis is growing. (J. H. Hutton: *Radiology* 24:330 (Mar.) 1935; J. H. Hutton, W. L. Culpepper and E. C. Olson: *Arch. Phys. Therapy* 17:7 (Jan.) 1936; W. A. Selle, J. J. Westra, and J. B. Johnson: *Endocrinology* 19:97 (Jan.-Feb.) 1935; E. Merle: *Bull. et mém. Soc. méd. d. hôp. de Paris* 51:35 (Jan. 21) 1935; J. Piéri and P. Sarradon: *Ibid.* 51:1579 (Dec. 2) 1935; S. S. Altshuler and S. E. Gould: *Ann. Int. Med.* 9:1595 (May) 1936; L. Cannanò: *Policlinico (Sez. prat.)* 43:1099 (June 15) 1936; H. Chabanier, P. Puech, C. Lobo-Onell and E. Lélou: *Presse méd.* 44:986 (June 10-17) 1936). While an attempt to imitate Houssay in human

diabetics without hypophyseal disease cannot be commended, the result as regards correction of cases with supposed hypophyseal hyperfunction may be awaited with somewhat skeptical interest.

Certain theories have long associated the *thyroid* with diabetes, and recent work has traced relations between the thyroid and hypophysis. Houssay, Bissotti and Rietti found that anterior pituitary extract still produces hyperglycemia and glycosuria after thyroidectomy. Simple thyroidectomy increases the susceptibility to insulin hypoglycemia. The clinical relationships of thyroid disorders and diabetes have been extensively reviewed by Joslin and Lahey and others. All the evidence, clinical and experimental, confirms the established doctrine that thyroid excess, with its accompanying intoxication and elevated metabolism, can aggravate an existing diabetes and activate a latent diabetes, and that removal of the disturbing thyroid factor by surgery, or otherwise, can markedly ameliorate the diabetes in such a case. At the same time there is no evidence that the thyroid is a primary cause of diabetes; experimental diabetes following pancreatectomy is not checked by thyroidectomy, except as the mere quantity of sugar may be reduced by slowing of the total metabolism; clinical diabetes can coexist with spontaneous myxedema; and the trial of thyroidectomy for human diabetes (A. Rudy, H. L. Blumgart and D. D. Berlin: *Am. J. M. Sc.* 190:51 (July) 1936) has not proved beneficial.

One of the recent observations on\*the *adrenals* is that insulin sensitivity results from denervation of these glands, section of the splanchnic nerves or removal of the celiac ganglion (De Takats and Cuthbert; Ciminata).\* The newly discovered relations between the anterior pituitary and the adrenal cortex have been summarized by Evans, Collip and

others. A brilliant contribution to the theory of carbohydrate metabolism is the demonstration by C. N. H. Long and F. D. W. Lukens (*J. Exper. Med.* 63:465 (Apr.) 1936) that ablation of the adrenal cortex inhibits the diabetes following pancreatectomy in much the same manner as Houssay's hypophysectomy. The injection of anterior pituitary extract in the depancreatized-hypophysectomized animal results in a quick return of fatal diabetes, but does not produce this result in the animal from which pancreas and adrenal cortex have been removed. Long considered that the hypophysis exerts its influence upon carbohydrate metabolism through the adrenal cortex; also that the secretion of the cortex governs the formation of sugar from protein, while the action of epinephrine secreted by the medulla is limited to the formation of sugar from glycogen. Houssay believes in an independent action of the pituitary. Also, more recently, W. M. Parkins, H. W. Hays and W. W. Swingle (*Am. J. Physiol.* 117:13 (Sept.) 1936) have reported that the blood sugar of the totally adrenalectomized dog remains within normal limits, except in shock, and have concluded that the adrenal hormone *per se* is not concerned in carbohydrate metabolism.

Clinically, there has never been any demonstration of pathology in the adrenals or an excess of either the medullary or the cortical secretion as a factor in the etiology of diabetes. Rare instances of hyperglycemia in association with adrenal tumors have been known, but always in connection with other

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\*The increased sensitiveness to insulin hypoglycemia is a phenomenon mentioned very frequently in pluriglandular research. It should be noted that one way of producing such sensitiveness is by removal of the pancreas itself (Copp and Barclay, also personal observations). Therefore, this sensitiveness, which may be due to various nutritive or metabolic disturbances, should not be interpreted too positively as a proof of "antagonism" between glands.

symptoms of adrenal overfunction. On the other hand, diabetes has been known to coexist with Addison's disease (Gowen; Allan). The results of denervation of the adrenals (De Takats; Ciminata; Cierci) in human diabetics or irradiation of the suprarenal area (Langeron, Desplats and Béra) have not been convincing. J. M. Rogoff (J. A. M. A. 106:279 (Jan. 25) 1936) and J. M. Rogoff and H. W. Ferrill (Proc. Soc. Exper. Biol. and Med. 34:100 (Feb.) 1936) described a fatal case of Addison's disease following attempted denervation of the adrenals for diabetes.

In general summary, while the newer discoveries have shed much light upon the regulation of carbohydrate metabolism and the rôles of various glands, they have not shaken the established doctrine of the essential unity of diabetes and its characterization as a deficiency of the pancreatic islands. Irradiation or operation upon other endocrine glands is unjustified, except in cases of demonstrable disease in those glands. Possible future developments, including the liver, also the duodenum (G. G. Duncan, N. P. Shumway, T. L. Williams and F. Fetter: Am. J. M. Sc. 189:403 (Mar.) 1935) or jejunum (F. Rathery, A. Choay, and P. de Traverse: Compt. rend. Acad. d. sc. 203:206 (July 15) 1936) must be left without discussion. Up to the present there is no proof of any effective treatment of diabetes based upon any organ except the pancreas.

*Endocrine Factors in Fat Metabolism.*—Some evidence exists of an influence of the *hypophysis* upon fat metabolism (*cf.* Beck) and acetone body formation (*cf.* reviews by Collip and Evans). The latest discovery in this field, however, reveals a new function of the *pancreas*.

The experiments concerning hydropic degeneration (Allen, Martin, 1922) indicated that when the diabetes had

reached "total" severity after disappearance of all the beta cells, the animal nevertheless was very different from a totally depancreatized dog, and, the alpha cells of the islands persisted unchanged or with increased granulation. The question of the function of the alpha cells thus remained open. The possibility is also open that the other pancreatic elements, *viz.*, the acinar or the duct cells, may furnish an internal secretion.

Upon the discovery of insulin, all investigators who undertook to keep depancreatized dogs alive with it, found that the animals died after weeks or months with marked enlargement and fatty changes in the liver. Proof had been furnished by experiments, from Minkowsky down to Allen and Homans, that the external secretion of the pancreas has no specific relation to diabetes. Nevertheless, the later workers found that the feeding of raw pancreas prevented the fatty liver and enabled the dogs to live. Best and his associates (C. H. Best and H. J. Channon: Biochem. J. 29:2651 (Dec.) 1935; C. H. Best, Mawson Huntsman, M. E. McHenry, and E. W. and J. H. Ridout: J. Physiol. 86:315 (Mar. 9) 1936) attributed this result to *lecithin* and its decomposition product *choline*, which they found similarly efficacious.

L. R. Dragstedt, J. van Prohaska, and H. P. Harms (Am. J. Physiol. 117:175 (Sept.) 1936) have very recently corroborated the absence of connection between the external pancreatic secretion and diabetic sugar metabolism, their negative results from administration of 300 to 1100 c.c. of fresh pancreatic juice to dogs being comparable with those of Allen (Rockefeller Monograph, Chapt. IV, 1919) of feeding pancreas to patients or giving the hydraulically expressed juice of 2 Kg. of pancreas through a duodenal tube. All such ex-

periments have not yet prevented some physicians from trying to treat diabetes with pills supposed to contain pancreatic substance.

Dragstedt and his collaborators added the brilliant demonstration that the fatty liver is not due to absence of pancreatic juice from the bowel, because it does not occur in animals with a pancreatic fistula. The effect is due to something contained in the pancreatic tissue, because it is prevented by the feeding of pancreas, but not of fresh pancreatic juice. It is not attributable merely to lecithin or choline, because the amount of these substances found necessary by Best greatly exceeds that in the effective quantity of pancreas, also the feeding of brain tissue containing much more lecithin does not produce the result.

In a third paper these authors announced success in obtaining from alcoholic pancreas extract a substance named "*lipocaic*," which on oral administration prevents fatty liver and death in depancreatized dogs, and is believed to be a new pancreatic hormone concerned in some way with the transport and utilization of fat. There is no suggestion as yet concerning the possible usefulness of this product in either the liver disorders or the impaired fat absorption occasionally encountered in diabetic patients.

#### ***Diagnostic Tests with Glucose.***—

The REVIEWER, in 1913, called attention to the "paradoxical law" of glucose, according to which there is no absolute limit of glucose utilization in the normal body; utilization always increases with increased administration. On the contrary, diabetes involves a genuine limitation of utilization in proportion to its severity; furthermore, the diabetic impairment is the only one that is known to be aggravated by repeated administration of sugar. The application of this law was illustrated in normal animals,

and in those which were either diabetic or nondiabetic after removal of different portions of the pancreas, and various "diabetogenic" influences were thus tested. For example, fasting or carbohydrate-free diet seems superficially to lower the carbohydrate tolerance, as indicated by increased hyperglycemia and glycosuria after glucose administration; but repetition of the glucose feeding shows that the reduction of tolerance is only apparent and not real. Without confusion on account of this mere temporary state of unpreparedness, fasting was found useful as a treatment which actually increased the true tolerance in diabetes.

The importance of this state of preparedness of the pancreas, liver or other organs was further illustrated by the work of Hamman and Hirschman (1919) with repeated glucose ingestion, showing that in normal persons, after an initial dose followed by the usual slight hyperglycemia, a second dose gave rise to slighter hyperglycemia or none. Departures from this rule were exhibited by diabetics in proportion to the severity of their disease. In mild cases, with a large part of the normal assimilative power retained, there was some degree of lowering of the second blood curve as compared with the first; but as the diabetes became more pronounced, this response of the assimilative mechanism was lost more and more completely. This effect of glucose doses repeated at intervals of 20 minutes to several hours has been verified in different ways by a number of authors, including Staub (1921) and Traugott (1922). Inasmuch as these authors have added nothing essential to the original observations of Hamman and Hirschman, the German designation of this as the "*Staub-Traugott phenomenon*" should be dropped from the literature.

Exton and Rose (1934) introduced a diagnostic *test* based on the above principles, consisting in the administration of 2 doses of 50 Gm. ( $1\frac{2}{3}$  ounces) of glucose one-half hour apart. Three blood sugar analyses are taken, one before each dose and one-half hour after the second dose. In diabetics, the elevation resulting from the second dose is typically higher than from the first dose; in nondiabetic *vice versa*. Owing to the large literature which has made the test with a single dose of 100 Gm. ( $3\frac{1}{3}$  ounces) glucose a standard, this older method will doubtless continue to be extensively used; but while it suffices for diagnosis in the majority of cases, there are doubtful instances in which the method of repeated doses will give a clearer decision. While a uniform procedure like that of Exton is advantageous, the same principle can be applied in the form of a succession of high carbohydrate meals on one or a series of days, and this prolonged strain upon the assimilation will occasionally reveal a latent diabetes which is not positively distinguishable by a single ingestion of glucose.

It may become customary to make tolerance tests in all available blood relatives of any diabetic patient, because many diagnoses of unsuspected early cases can thus be made. This is one of the most feasible prophylactic measures for discovering and checking diabetes in its early latent stage.

**Prognosis.**—The death-rate from diabetes continues to rise steadily instead of falling, because of the greater number of cases recognized and also the various factors which bring about a genuine increase in the incidence of this disease. Joslin mentions that diabetes as a cause of death in the United States has risen from twenty-seventh place in 1900 to tenth place in 1933, and refers to Dublin's prediction that within 10 years diabetes

will equal tuberculosis as a cause of death. On the other hand, the prognosis for diabetic individuals has been demonstrably improved by treatment. Joslin analyzed his case records to show that the average duration of life from time of diagnosis of the disease, including all patients at all ages, was 4.8 years under the classical Naunyn treatment, 6.0 years in the time of undernutrition diets, 7.6 years in the early period of insulin treatment, and 11.0 years since 1930. The prognosis varies practically according to the treatment. Barring accidents and the consequences of incurable complications existing before treatment, it is possible with proper care for any average patient to live out as long a life as if he had never had diabetes. The fact that diabetics under the best conditions appear to live somewhat longer than the average expectancy of the general population is explainable by the healthful habits which the disease enforces. The essential fact is that today nobody need die of diabetes, and this assurance can truthfully be given to any patient at the outset of his disease. Joslin particularly points out that children, who notoriously succumbed early under the older treatment, no longer die of diabetes if correctly managed. These facts confirm previous statements that a fatal disease has been converted into a mere inconvenience. Though not yet curable, it is controllable with mathematical accuracy.

These potential results are not yet actually achieved for the vast majority of diabetics. The two chief causes of the unnecessary mortality are well known. One cause is the carelessness of many patients. A surprisingly large number of persons still defy the very mild restrictions of the present-day diabetic diet, and either refuse insulin or abuse it in the attempt to compensate for reckless eating. Such carelessness is actually encouraged by the removal of the former

fears of diabetes, but such persons need to be reminded that it is still a fatal disease if not controlled. The other cause of mortality should be recognized with equal plainness, *viz.*, faulty treatment by physicians who do not sufficiently understand the disease or who lack adequate facilities for observing and training patients. Diabetic treatment, like surgery, is open to every physician who will take the trouble to acquire the necessary skill in it. There is a surgical conscience which generally prevents the undertaking of difficult operations by those not well qualified, except under conditions of necessity. There is today a far higher death-rate from unskilled diabetic treatment than from unskilled surgery, and surgeons are among the offenders. Physicians, under the impression that anybody can give insulin, can reduce the excess diabetic mortality by paying attention to facts which were evident at the beginning of the insulin era (Allen and Sherrill). Insulin has tremendously improved diabetic treatment, but has not simplified it. Insulin is a literally epoch-making discovery, which revolutionizes the results of diabetic treatment when properly employed, but it cannot atone for lax or inadequate dietary methods.

**Causes of Death.**—The causes of diabetic deaths and the changes occurring in consequence of the advent of insulin are best illustrated by Joslin's careful statistics.

*Coma* was formerly the leading cause, accounting for 63.7 per cent. of all deaths under the classical Naunyn treatment, falling to 41.6 per cent. with the introduction of undernutrition, and dwindling to 6.1 per cent since 1930. This change is clear evidence of the successful use of insulin by physicians for both preventing and treating coma, but Joslin properly stresses the fact that practically every coma death is avoidable under

right conditions and further progress in the elimination of coma is possible with effort and education.

*Tuberculosis* is held accountable for only 4.9 per cent. of diabetic deaths in the Naunyn period, and this figure has remained practically unchanged up to the present, though it is enormous reduction below older statistics. Root reported 245 cases of pulmonary tuberculosis recognized among 9474 diabetic cases between 1898 and 1932. Every observer can testify that the danger from tuberculosis has been lessened by every advance in diabetic treatment, and particularly insulin has made a spectacular revolution, by enabling the patient to assimilate liberal diets. Its effect in building up weight and strength are so remarkable that it is coming into use for some types of nondiabetic tuberculous cases. (F. M. Allen, S. A. Douglass, E. L. Warren, and W. E. Pottenger: *Am. Rev. Tuberc.* 34: 257 (Aug.) 1936).

*Other miscellaneous infections* accounted for 7.4 per cent. of the deaths in Joslin's series in the Naunyn period, 12.7 per cent. in the undernutrition period, 16.6 per cent. in the early insulin period, and 12.4 per cent. since 1930. This increase is evidently explained largely by the fact that patients who are spared from coma may live to fall victims to some chance infection. It is also true that laxity or imperfectly treated diabetes predisposes to all sorts of infectious dangers. Among cases under less careful treatment than Joslin's there is undoubtedly a much higher infectious mortality, and this can be decidedly reduced by better management, especially before the infection develops.

*Cardio-renal-vascular disease* has risen from a minor position, *viz.*, 17.5 per cent. in the Naunyn period, to 55.8 per cent. since 1930, thus replacing coma as the cause of the majority of all diabetic deaths. In this group, *gangrene* holds

only a subsidiary place, accounting for 7.7 per cent. of all diabetic deaths. *Apoplexy* outranks it by causing 10.7 per cent. of deaths, while the highest place in the group is held by *cardiac complications* with 30.2 per cent. of the total mortality. This is a far greater increase than can be attributed to the mere increase of longevity of patients, and it is further discussed under the subject of treatment.

**Treatment.**—The methods of practical diabetic treatment still consist in the use of diet and insulin.

**IDEAL AND PURPOSE.**—The writer believes that the purpose of treatment should be to restore a patient's abnormal condition as nearly as possible to normal. This standard demands normal blood as well as urine. Although this view is probably supported by a preponderance of opinion, a number of highly qualified specialists still take an opposed stand, on the ground of absence of observed harm from prolonged hyperglycemia, though any important reason for preferring an abnormal state seems not clear. Joslin writes: "The urine is to be made sugar-free and the blood sugar normal." As his reasons, he gives: "(1) because normal values are obviously the best; (2) because a high blood sugar is a stimulus for insulin secretion and the impaired island tissue should be spared overwork." He properly doubts the chemical action of a high sugar content of the blood or tissues as directly causing any of the complications. The present REVIEWER has always insisted on normal blood sugar as the most delicate criterion of control of the diabetes.

The nature of diabetes is an impairment of normal metabolism and hence of tissue nutrition. This specific impairment of nutrition, which has nothing to do with the mere quantity of food eaten or metabolized, is probably the funda-

mental cause of the lowered resistance and of all the complications of diabetes. Other chemical abnormalities are known, for example, lipemia and particularly increase of cholesterol; but with any rational form of diet a normal blood sugar gives assurance that, barring complicating conditions, the chemistry will be otherwise normal.

Another consideration of practical importance is that the approval of high blood sugar and sometimes slight glycosuria by specialists tends to encourage carelessness among the great mass of physicians and their patients, who will often encounter very serious harm or danger thereby. The maintenance of approximately normal conditions is feasible in nearly all cases, and the stricter care necessary for this purpose, instead of being an argument against, is a reason in favor of it.

**DIET TREATMENT.**—The high fat diets have lost their widespread vogue. They were either an attempted return to high calory rations, in defiance of the proved principles of caloric limitations, or else they depended for their result (notably in the work of Newburgh and Marsh) essentially upon caloric restriction. The opposite wave of high carbohydrate diets (E. M. Sorkin and E. Y. Reznitskaya: *Klin. med.* 13:977 (July) 1935; M. Krakauer: *Klin. Wchnschr.* 14:820 (June 8) 1935; B. W. Ercklentz: *Deutsche med. Wchnschr.* 61:1911 (Nov. 29) 1935; I. M. Rabinowitch: *Canad. M. J.* 33:136 (Aug.) 1935; H. R. Geyelin: *J. A. M. A.* 104:1203 (Apr. 6) 1935; F. B. Peck: *Am. J. M. Sc.* 192:697 (Nov.) 1936; W. D. San-sum: *South. M. J.* 29:414 (Apr.) 1936) seems likewise to be subsiding. The broad result of this clinical experimentation has been a confirmation of the fact originally demonstrated by the REVIEWER together with Sherrill, that isocaloric interchanges of protein, carbohydrate and

fat are possible on a wide scale, with comparatively slight changes in the insulin requirement.

Sansum has correctly shown that certain patients feel better with liberal carbohydrate allowances. For these and for certain complications (nephritis, cirrhosis) amounts above 200 grams daily are permissible. High proportions of carbohydrate within proper limits of total calories as used by Rabinowitch, are not objectionable when the blood sugar is controlled. The tendency to curative effects through stimulation of the islands of Langerhans, as claimed for example by Porges, has not been substantiated. Likewise, the assertions of Geyelin rest upon fallacious tests of the mere quantity of carbohydrate assimilated under different conditions, and upon lack of understanding of the principle of caloric regulation either before or after the introduction of insulin. On the other hand, fat diets have not been shown to damage the island function, beyond their mere caloric value. The apparent lowering of sugar tolerance following high fat diet is, like the influence of fasting, a temporary incidental phenomenon which has been misjudged on the basis of brief tests and has nothing to do with the true tolerance. In general, excessive amounts of carbohydrate make the blood sugar somewhat more difficult to regulate, and excessive proportions of fat predispose to lipemia and acidosis, especially in the event of any accidental disturbance.

The overwhelming influence of the total calories and body weight can easily be confirmed by any observer who will make suitable experimental changes in them over a sufficient length of time. There is a very wide leeway in the choice of the proportions of the individual foodstuffs, according to the preference of individual physicians or particularly the needs of individual patients.

The REVIEWER has at no time seen any reason to depart from the conclusion reached in 1922: "The case records will show that, except for experimental purposes, we have not used seriously one-sided diets. No fixed rules of protein requirement or ketogenic-antiketogenic balance have been followed. The principle has merely been to give a thoroughly safe sufficiency of both protein and carbohydrate while avoiding excesses. Thus, for a diet of 2000 calories, we have commonly allowed 100 Gm. protein and 100 to 150 Gm. carbohydrate." The later and more moderate advocates of high carbohydrate do not depart greatly from this rule. Thus, Peck favors high carbohydrate, but states that the average carbohydrate in his diets is 180 grams daily.

INSULIN.—*Dosage and Timing.*—It is still the rule to avoid the use of insulin when the diabetes can be controlled efficiently and comfortably by diet alone. The custom of some physicians of prescribing insulin indiscriminately to practically all diabetics, frequently with minimal attention to diet, should be condemned. The REVIEWER is also opposed to the use of luxus diets, as by Geyelin, with correspondingly excessive insulin dosage. Unrestricted or "free" diets (Ercklentz), with attempted protection by high insulin dosage, appear likewise as a step in the wrong direction. Specialists mostly agree that the diet should be planned so as to keep the insulin dosage reasonably low, and the body weight for this purpose should be not above, but rather a few pounds below the average for the individual.

The majority of physicians have not given enough attention to the effective *timing* of insulin doses to suit individual needs. The REVIEWER, in 1924, was the first to recommend this procedure; for example, the giving of the morning insulin in some cases an hour or more



before breakfast, and other doses at such intervals as were found most effective for smooth regulation of the sugar. The desirability of proper individualized timing of doses has since been emphasized by others, most recently by A. Sindoni, Jr. (Arch. Int. Med. 57:949 (May) 1936).

The *day and night fluctuations of blood sugar* have recently been given a deeper significance, especially by European authors. One of the latest papers, by R. Hopmann and H. Martini (Ztschr. f. klin. Med. 129:70, 1935), divides patients into "morning" and "midday" types according to the time of their maximum hyperglycemia, and recommends the giving of insulin 1 to 1½ hours before breakfast for the former type. Superficially, it might be assumed that the former are merely the severe cases, with a rise of endogenous sugar during the night without food or insulin; while the latter are the milder cases, with hyperglycemia produced chiefly by food but reduced somewhat toward evening by reason of a partial response of the pancreas to stimulation in the Hamman-Hirschman manner. The actual interpretation, however, is in support of Forsgren's doctrine (J. Möllerström: Upsala läkaref. förh. 41:287 (June 6) 1935; E. Forsgren: Nord. med. tidskr. 11:937 (June 6); 12:1134 (July 11) 1936) of alternating assimilative and dissimilative phases of liver function. This conception, that the liver has a rhythmic cycle of activity, one phase being dominated by dissimilative processes such as bile production, and the other by assimilative processes such as glycogen storage, is now attracting increasing interest and support. These phases are said to be illustrated by the higher sugar curves in tolerance tests between 3 and 7 A. M. (dissimilative period), as compared with those between 1 and 4 P. M. (assimilative period). These dif-

ferences are shown to be independent of the previous diet, sleep, exercise, and other known variables. If finally established, this theory promises to be important as regards not only diabetic phenomena, but also the correlation with general physiology.

**PROTAMINE INSULINATE.**—The discovery of the protamine-insulin compound and its introduction in diabetic treatment was described by Hagedorn and collaborators, also in a monograph by Krarup. On the basis of 15,000 blood sugar determinations and other clinical and chemical studies on a corresponding scale, it was demonstrated that the effect is prolonged for at least 12 hours, or about twice as long as with ordinary insulin. This effect is actually due to delayed absorption, as Longwell has since determined that with intravenous injections in rabbits there is no significant difference between the effect of protamine and of ordinary insulin upon the blood sugar.

Records and curves are presented to show the results of treatment with 1 or 2 doses of protamine insulin in the 24 hours, and also combinations, especially the use of ordinary insulin in the morning and protamine insulin in the evening.

The papers of later writers have been concerned essentially with confirmations of the Danish work, and with variations of the arrangement of diet and insulin doses. The diets of the Hagedorn group, though adapted to different individual needs, were of the general order of 70 grams protein, 100 grams carbohydrate, and 2300 calories. The Root group in Joslin's clinic gave higher carbohydrate, 130 to 241 grams per day. Also the division of the carbohydrate was different, the distribution in the 3 meals being with the Danish group  $\frac{2}{5}$ ,  $\frac{2}{5}$ ,  $\frac{1}{5}$ , while with the Boston group it was  $\frac{1}{5}$ ,  $\frac{2}{5}$ ,  $\frac{2}{5}$ . Campbell and associates agreed with the Danish group in regard to the

lower carbohydrate, because of the difficulty of controlling the blood sugar after high carbohydrate meals (H. C. Hagedorn, B. N. Jensen, N. B. Krarup, and I. Wodstrup: *J. A. M. A.* 106:177 (Jan. 18) 1936; N. B. Krarup: *G. E. C. Gad*, Copenhagen, 1935; H. F. Root, P. White, A. Marble, and E. Stotz: *J. A. M. A.* 106:180 (Jan. 18) 1936; R. B. Kerr, C. H. Best, W. R. Campbell, and A. A. Fletcher: *Canad. M. A. J.* 34:400 (Apr.) 1936; R. M. Wilder: *Proc. Staff Meet., Mayo Clin.* 11:257 (Apr. 22) 1936; R. G. Sprague, B. B. Blum, A. E. Osterberg, E. J. Kepler and R. M. Wilder: *J. A. M. A.* 106:1701 (May 16) 1936; E. P. Joslin, H. F. Root, A. Marble, P. White, A. P. Joslin, and G. W. Lynch: *New England J. Med.* 214:1079 (May 28), 1936; H. Bowcock: *South. M. J.* 29:701 (July) 1936; B. Smith: *California and West. Med.* 45:144 (Aug.) 1936; I. M. Rabinowitch, A. F. Fowler, and A. C. Corcoran: *Canad. M. A. J.* 35:124 (Aug.) 1936; E. P. Joslin: *Ann. Int. Med.* 10:179 (Aug.) 1936; I. M. Rabinowitch, J. S. Foster, A. F. Fowler, and A. C. Corcoran: *Canad. M. A. J.* 35:239 (Sept.) 1936; E. P. Joslin: *Minnesota Med.* 19:570 (Sept.) 1936; T. I. Bennett and A. M. Gill: *Lancet* 2:416 (Aug. 22) 1936; F. M. Allen: *J. A. M. A.* 107:430 (Aug. 8) 1936).

There is as yet no uniform plan or *timing* of the protamine insulin doses, and they will presumably need to be varied to suit individual requirements. Injections 30 to 90 minutes before breakfast, and at various times from 3 P. M. on into the evening, are mentioned. One noteworthy point is the extremely poor control of the blood sugar, as shown in the curves with ordinary insulin in most of the reports. Are these actually representative of the results obtained by these authors heretofore, and would they

have confessed to them prior to the advent of the new insulin?

Criticisms seem possible: (1) The results with the new insulin have not generally been compared with the best results obtainable with the old insulin, for though control may be easier with the new insulin it can still be achieved with the old form to a much better degree than is illustrated in the recent papers; (2) in exceptionally difficult and labile diabetic cases, the difficulties with the new insulin seem to have been minimized, and it may be predicted that these difficulties, as described recently by the REVIEWER, will call for increasing consideration in the future.

An entirely different attack upon this problem is represented by the so-called crystalline insulin (M. P. Mains and C. J. McMullen: *J. A. M. A.* 107:959 (Sept. 19) 1936); H. A. Freund and S. Adler: *Ibid.* 107:573 (Aug. 22) 1936), prepared in a water-clear solution, and exerting its effect over a period of time intermediate between that of the regular insulin and protamine insulin.

The short list of papers on this general subject to date will doubtless grow to a large mass very soon, and it may be hoped that Hagedorn's brilliant accomplishment will lead the way to still further advances in diabetic therapy.

**Treatment of Complications.**—*Heart Disease* (T. Leary: *J. A. M. A.* 105:475 (Aug. 17) 1935). Reports in recent literature concerning dangerous consequences of insulin in cardiac cases, though correct in details, have unduly alarmed many physicians. As hypoglycemia may sometimes be fatal in cases of coronary disease, it should be guarded against in such cases, even at the price of allowing the blood sugar to remain moderately elevated. Also, insulin reactions are not intentionally produced in any heart ailment. Nevertheless, the writer strongly agrees with Joslin that

the heart needs the power to utilize sugar, all the more because of being diseased. It is not true that there is any extreme danger in the proper use of insulin in ordinary heart cases, even of severe type, and insulin reactions are generally withstood safely. When the diabetes is actually too severe to be controlled effectively by diet, the benefits of skillfully used insulin far outweigh the risks. The theory that high blood sugar helps the nutrition and function of the heart is fallacious, because hyperglycemia is a stimulus only when it represents a liberal glucose supply together with normal assimilation. Hyperglycemia due to impaired assimilation is detrimental to the heart as well as to other organs, and the heart function is often perceptibly improved when insulin reduces a diabetic hyperglycemia to normal.

*Treatment in Relation to Arteriosclerosis.*—The admirable observations and review by Leary presented the strongest argument for the rôle of high blood cholesterol in the etiology of arteriosclerosis. On the other hand, the experimental basis, especially as regards a genuine reproduction of human atherosclerosis by cholesterol feeding in animals, is subject to attack (Jobling and Meeker). More definitely convincing is Landé and Sperry's study of 123 autopsies following sudden (chiefly accidental) deaths of persons with various degrees of atherosclerosis. The range of the serum cholesterol was within normal limits, and no relationship was found between it and the lipid content of the aorta. Such evidence tends to upset the chief foundation of high carbohydrate diet for diabetes, *viz.*, the threat of arteriosclerosis.

The impaired nutrition of the blood vessels with inadequately controlled diabetes still appears as the most probable source of susceptibility to injuries of all kinds, and thorough control of the di-

abetes with any form of diet as the one dependable safeguard against all complications. Furthermore, it is well known that arteriosclerosis occurs most frequently with mild rather than severe diabetes, because of the long duration. The management of great numbers of diabetic cases by partial measures, just sufficient to preserve temporary comfort, merely converts severe into mild diabetes, and provides a host of candidates for future arteriosclerotic complications. This inadequacy of treatment, therefore, and not the mere increase of longevity, is mainly responsible for the increasing mortality from gangrene and other vascular lesions.

**HYPOGLYCEMIA.**—Except for the discovery of insulin and the hypoglycemia resulting from its overdosage, it is difficult to estimate how long delay there might have been in the recognition of a morbid entity never before diagnosed in medical history, *i. e.*, *spontaneous hypoglycemia*. This condition was first described by Harris (1924) under the name "*spontaneous hyperinsulinism*." It has subsequently been learned that reduction of the blood sugar, even to a fatal extreme, can occur from causes not connected with insulin, *e. g.*, after removal of the liver or in rare instances of liver disease. Genuine hyperinsulinism has been most typically demonstrated in cases of tumors of the islands of Langerhans, likewise in cases of pituitary disease associated with hyperplasia of the pancreatic islands. Some clinical cases of hypoglycemia still remain uncertain in etiology.

The *treatment* necessarily varies with the cause, and the success is correspondingly variable. The symptomatic treatment for the typical attacks of weakness, tremors, unconsciousness, convulsions, etc., is naturally the administration of sufficient quantities of **glucose** by stomach or vein. The most decisive

cures are those obtained when the **surgical removal of islet tumors** has been possible (H. Frank: *München. med. Wchnschr.* 82:1829 (Nov. 15) 1935; E. J. Kepler and W. Walters: *Proc. Staff Meet. Mayo Clin.* 11:454 (July 15) 1936; E. H. Rynearson: *Ibid.* 11:451 (July 15) 1936; S. H. Liu, H. H. Loucks, S. K. Chou and K. C. Chen: *J. Clin. Investigation* 15:249 (May) 1936). In cases without discoverable tumors, the resection of portions of the pancreas has sometimes proved unavailing, either because the hypoglycemia was

of some other origin, or because the portion of the pancreas containing the actual tumor (which may be very small) was missed. Medical treatment consists chiefly in diet; and as high carbohydrate diets have brought no improvement or perhaps actual aggravation, **high fat diets** have been used because of the demonstrated action of high fat rations in producing prolonged hyperglycemia. John treats hypoglycemic cases by giving **insulin**, in the attempt to repress the spontaneous production of insulin by the patient's pancreas.

## SURGERY AND DIABETES

By HOWARD F. ROOT, M.D.

The increasing importance of the treatment of diabetes during its surgical complications has been recognized during 1936 in a number of publications dealing with the subject. In the French literature should be mentioned monographs by H. Chabanier, C. Lobo-Onell and E. Lelu (*Diabète et Chirurgie*. Masson, Paris, 1936), F. Fredet and G. Jeanneney ("La Chirurgie chez le Diabétique," Paris, 1936) and F. Rathery (*Le traitement des Gangrenes Diabétiques*, Bailliere et fils, Paris, 1936). The first authors, writing from a large experience with diabetes in Paris, give special attention to *postoperative collapse*. They have observed this postoperative critical state of shock or collapse with low blood-pressure and anuria in diabetic patients and compared it with a similar state of collapse in nondiabetics. They hold that in nondiabetics in postoperative collapse, there is observed with decreasing urine secretion, a rise in the blood urea nitrogen and a fall in the plasma CO<sub>2</sub> combining power similar to what occurs in a diabetic, but to a less marked degree. In a diabetic, in addition, there will be marked ketosis, a more noticeable fall

in the CO<sub>2</sub>, and coma may even develop along with diminished urine secretion. In both types of patients they feel that fundamentally there is a disturbance of the acid-base relationship and failure in kidney function, but in a diabetic patient the situation becomes much more grave, owing to the fact that the failure in carbohydrate metabolism greatly accentuates the degree of acidosis and, therefore, the degree of kidney failure. They emphasize the use of **salt solution and glucose solution given parenterally with insulin at the time of operation** to avoid postoperative shock.

Fredet and Jeanneney (*loc. cit.*) recognize the importance of products of a nitrogenous nature resulting from destruction of cells, due to bacteria and disorders of kidney function, as important features in surgical diabetics, influencing development of acidosis.

Rathery (*loc. cit.*) from a large service in Paris, speaks of the influence of *bacterial toxins* on the tendency of diabetic patients with surgical conditions to be rather resistant to insulin. In the surgical patient with severe complications, diminished chloride in the urine is

associated with hypochloremia, again an important factor predisposing the diabetic to acidosis and coma. R. Boulin ("Extrait de l'Encyclopedie Medico-Chirurgicale" 10:510, p. 2, 1936), in his section on gangrene, summarized the French viewpoint with regard to the cause of *diabetic arthritis*. Under the leadership of Marcel Labbe the metabolic background of premature and excessive arteriosclerosis seems to be accepted. Hypercholesteremia and hyperglycemia are more or less constant findings; whereas increases in the blood calcium they regard as inconstant and of little importance, because it gives little clue to the state of the calcium metabolism in the tissue. Labbé's (Labbé, Boulin, Justin-Besançon and Desoile: La Presse Thermale et Climatique, (Apr. 15) 1936) most recent publication is cited. Although arteriosclerosis is regarded as fundamental in the development of *gangrene*, they speak also of gangrene due to nervous causes with, however, the statement that it is a very rare form. Ordinarily, in the REVIEWER's experience the "*mal perforant plantaire*" is explainable on the basis of constant pressure with callus formation, deficient blood supply, and infections.

These articles are written with the typical French clarity, but one conspicuous omission is noticed. No statistical analysis of cases or case records is presented.

The attitude toward diabetic surgery taught in the diabetic clinic of Umer at the Westend Hospital, Berlin, is expressed in an article by Storrang (Med. Klin. 32:1589, 1936). The value of **insulin** in the treatment of surgical diabetics was early emphasized by Umer and among 7,000 diabetics treated with insulin in his clinic since its discovery, several reports of groups of surgical cases have been published. An important fact is that no deaths from coma have

occurred in any of these surgical cases. Since 1924, the method of "überinsulinierung" has been employed. The urine has been made sugar-free with insulin, the doses increased daily by 4 to 8 units at a time until the blood sugar is normal. Often with this energetic treatment *insulin edema* occurs, especially after acidosis and diabetes made severe by infection. Since a gain of 10 kilograms in edema would overstrain a weak heart, it must be combatted by a **salt-free diet**, **cardiac** remedies or diuretics. In *acute surgical emergencies* he gives 20 to 40 units of **insulin** and at the same time, intravenously, 80 to 100 c.c. of 25 per cent. **glucose solution** immediately before the operation. Minor surgical procedures are carried out while the patient remains in the diabetic ward. When patients have to transfer for major surgical, their metabolic and diabetic treatment is continued under the direct charge of the physicians in charge of the diabetic ward.

*Anesthesia* is produced in various ways. **Spinal anesthesia** is used for surgery of the extremities. For short periods of narcosis, the intravenous administration of "**eunarcon**" is favored. The use of chloroform is deplored.

L. G. Herrmann ("Passive Vascular Exercises," J. B. Lippincott Co., 1936) has summarized a history of the attempts to improve the blood supply in the legs of patients with *vascular disease*. The work of the preceding 100 years leading to the apparatus which he so skillfully devised to provide alternate suction and compression in an attempt to improve the blood flow is summarized. A number of authors have confirmed the excellent results obtained with the **Pavaex apparatus** in acute embolic conditions. With diabetic patients with gangrene or infection, it is still not quite certain what place this form of treatment will have in the future. He emphasizes the

importance of continuing the best possible treatment of the diabetes and of cardiac function. A new principle has been employed by W. S. Collens and N. D. Wilensky (Am. Heart J. 11:705 (June) 1936) for the treatment of vascular lesions of the extremities, which he calls "**reactive hyperemia**." During this stage the skin is flushed with the flow of blood and it seemed that a marked dilatation of small vessels occurred. In 1932, Schede and Bettmann used a somewhat similar method for the treatment of vascular disease and particularly to improve the circulation around a joint. Collens has devised an apparatus which is now available and has reported the improvement of chronic, slow-healing lesions even in *diabetic feet*. It is very difficult to evaluate new methods of treatment in lesions of diabetic feet. Everyone who sees a large number of cases finds that results improve in many series of cases directly in proportion to the amount of interest, time and energy spent in applying treatment.

Sir Thomas Lewis has published a new volume ("*Vascular Disorders of the Limbs*," The MacMillan Co., New York, 1936) which will be found of great value to anyone interested in the study of any phase of the problem of *vascular disorders of the limbs*. He gives no statistical discussions of any group of cases, but clear and concise descriptions of various types of disorders with the means of their study in order to establish diagnosis. Methods of treatment are described briefly.

In a summary of 1,002 operations performed at the New England Deaconess Hospital between January 1, 1928, and January 1, 1936, L. S. McKittrick (J. M. Soc. New Jersey (Sept.) 1936) lists 571 operations for the *lower extremities*, and 55 upon the *upper extremities*. The remainder of the operations were varied, with *abscesses* and *carbuncles* providing 140 and of the *gall-bladder region* 54 cases. Mortality rates are charted by years and show on the whole a downward tendency, but he has pointed out that there may be a deviation of mortality from one year to the next of 6 to 22 per cent. This is a fact of great importance to be borne in mind when a new form of treatment is being tried out. The cases come for treatment with such different degrees of severity and infections, that one year a new form of treatment may receive the credit for success which really should belong to the fortunate chance that in that year a less seriously infected group of cases was treated.

*Infections of the hand* received a good deal of attention in McKittrick's paper. He found 60 patients at the Massachusetts General Hospital and the New England Deaconess Hospital between 1923 and 1936 who had operations for infections in the upper extremities. The mortality was 8 per cent. Of these 60 patients, 27 lost all or part of one or more fingers, and in 5 amputations above the forearm were necessary. No infection of a finger in a diabetic is ever to be regarded as trivial and usually it will warrant treatment in a hospital.

## HYPERINSULINISM AND DYSINSULINISM

By SEALE HARRIS, M.D.

### PITUITARY, THYROID AND ADRENAL HYPERINSULINISM.

—Experimental studies and reports of cases by capable clinicians seem to show

that the endocrine glands are equally important etiological factors in the recently recognized disease entity, *hyperinsulinism*—the antithesis of *hypoinsulinism*

(diabetes mellitus). It is timely to review the data upon which is based the evidence that the pituitary, thyroid and adrenals may at times be the primary organs involved in the production of spontaneous hypoglycemia (endogenous hyperinsulinism).

**Interpretation of Experimental Data.**

—The interpretation, or the evaluation, of the wilderness of experimental data, often contradictory and paradoxical, on the relationship of the pituitary, thyroid, and adrenals to the insulin apparatus of the pancreas, in order to make it utilizable by the physician who must treat diabetes mellitus and the opposite condition, *i. e.*, hyperinsulinism, is a fascinating study, though it seems an impossible task at this time. It is evident that the investigators have only “scratched the surface” in knowledge of the interrelations of the endocrine glands and the rôle that the pituitary, thyroid and adrenals play in carbohydrate metabolism. Nevertheless, clinicians, with a few exceptions, agree that the organs of internal secretion have functions synergistic with, or antagonistic to, each other. Thus, the pituitary, thyroid and adrenals work in harmony with each other; and all of them are antagonistic to insulin secretion or to insulin utilization. Hyperpituitarism, hyperthyroidism and hyperadrenalinism are associated, and hypopituitarism, hypothyroidism and hypoadrenalinism are found together. When there is excessive secretion either of the hypophysis, thyroid, or adrenals, there is deficient secretion, or ineffective utilization of insulin, with hyperglycemia, glycosuria and a tendency to ketosis; and with hypopituitarism, hypothyroidism or hypoadrenalinism there is excessive and unrestrained secretion, or a relative excess, of insulin (hyperinsulinism), with the protean manifestations of hypoglycemia.

**Pituitary Hyperinsulinism.**—In 1912, Cushing observed that the ablation of the pituitary in animals was followed by a condition which he then called *hypophysia priva*, in which the animals developed severe degrees of usually fatal hypoglycemia. He then attributed the condition to the deprivation of hypophyseal secretion.

Cowley in 1931 proved that the blood of hypophysectomized dogs had a hypoglycemic action. Cowley concluded: “The increased tolerance to carbohydrates in hypofunction of the hypophysis, or in partial or total hypophysectomy, and hypersensibility to insulin after hypophysectomy, might be explained as due to an increase of insulin content in the blood following the decreased functioning of the hypophysis or its surgical extirpation.”

Mahoney experimenting on hypophysectomized dogs, proved that the condition of hypophyseopriva can be ameliorated or relieved by the administration of glucose. He, therefore, is convinced that hypoglycemia is responsible for the symptoms that follow ablation of the hypophysis.

Cushing, in 1933, in his Harvey Society lecture, said: “All things considered, therefore, evidence abounds that the high tolerance for carbohydrates in hypopituitary states is due to an increase of the insulin content of the blood due to withdrawal of the counteractive anterior lobe principle.” In a recent personal letter, Cushing states: “Unquestionably all the old states that we originally described as hypophyseopriva in dogs after hypophysectomy were due to hyperinsulinism though we had no means of determining this in years gone by.”

Cushing has described very graphically the relationship of the pituitary to the thyroid, adrenals and pancreas. He shows that with hyperpituitarism there is not only hypertrophy of the hypo-

physis, but enlargement of the thyroid, adrenals and thymus, though as yet there is no proof that the latter has any bearing on carbohydrate metabolism; and that in hypopituitarism the hypophysis atrophies and along with it the thyroid, adrenals and thymus become smaller in size. J. B. Collip's thyrotropic and adrenotropic hormones confirm Cushing's opinion that the thyroids and adrenals hypertrophy with the hypophysis; but the atrophy of the thyroids and adrenals coincidental with atrophy of the hypophysis may not be explained entirely by antitropic hormones.

K. J. Anselmino and F. Hoffmann show that an anterior pituitary extract increases the size and number of the islands of Langerhans in the pancreas of the rat. They believe that this effect is due to a specific pituitary hormone, for which they suggest the name of "*pancreatrophic substance*." With the use of the "pancreatrophic substance" in the rat, liver glycogen disappears almost completely. Anselmino and Hoffmann conclude that this hormone stimulates the insulin production of the islands of Langerhans. Their work has not yet been confirmed by others.

Evans and Houssay believe that the anterior lobe of the pituitary controls carbohydrate metabolism; that so long as the secretions of the pituitary and the islands of Langerhans are in balance, the blood sugar levels remain within normal limits, but that an excess of pituitary secretion inhibits the secretion of insulin, resulting in hypoinsulinism (diabetes mellitus). The converse is true that a deficiency of the secretion of the anterior lobe allows more or less unrestrained secretion of insulin (hyperinsulinism), of which hypoglycemia is a manifestation.

M. A. Goldzieher (Endocrinology 20: 86 (Jan.) 1936), in reporting 112 cases of chronic hypoglycemia estimated that

88 cases showed evidences of hypopituitarism. In this group there was 1 case of Simmonds' disease, 1 basophile adenoma, 14 cases of adiposogenital dystrophy, while the others were "characterized by typical fat distribution, postural hypotension and inadequate rise of the basal metabolism rate after a protein meal, typical blood picture and dysplasia of the cranium on x-ray examination." Goldzieher's treatment consisted of **organotherapy** and **dietary measures** suited to the needs of the individual patient, giving largely 5 and 10 per cent. carbohydrates, with 6 daily feedings. In the pituitary group he combined injections of a **fresh anterior lobe extract**. He reports that the hypoglycemia disappeared gradually after a few weeks' treatment. In one of Goldzieher's hypopituitary cases an operation was performed but resection of two-thirds of a normal pancreas failed to give relief from the symptoms.

**Thyroid Hyperinsulinism.**—It seems definitely settled that accelerated thyroid secretion, by increasing metabolism, releases glycogen from its repositories in the liver, probably through the synergistic glycogenolytic action of the thyroid with the adrenals. It is also evident that when there is hypothyroidism, a decreased amount of glycogen would be released from the liver and hypoglycemia would result, particularly with a normal pancreas, under which conditions there would be relative hyperinsulinism.

Zondek, in his recently published book on "Endocrine Disorders," discusses the interdependence of hormonal glands, stating: "The thyroid gland and the islet system of the pancreas inhibit each other. As thyroid function is diminished or ceases, the islet system obtains relative or absolute predominance. Since the extent of carbohydrate assimilation depends upon islet function, sugar toler-



ance is abnormally increased in thyroidectomized animals and myxedematous individuals."

J. P. Costello (J. Missouri M. A. 33: 88 (Mar.) 1936) reported a case of *cretinism with hypoglycemia*. His patient, a child 10 years old, weighed only 22 pounds, and presented the clinical picture of cretinism. She had frequent and recurring attacks of convulsions resembling epilepsy. The patient, when given thyroid extract and sugar, 5 ounces (150 Gm.) a day, improved remarkably, and likewise the blood sugar readings were higher. Costello was of the impression that in this patient the pancreas was overfunctioning, due to lack of the antagonistic effect of the thyroid. He found that there was only a temporary rise of the blood sugar when the glucose was added to the diet of his patient, in whom he believed there was a complete emptying of the stores of glycogen in the liver, which is common in hypothyroidism. Costello advised blood sugar studies on all cretins and other cases of hypothyroidism.

H. Marx, of the University of Berlin (Deutsche med. Wchnschr. 62:843 (May 22), 1936), reported a case of *myxedema* in a woman age 53 in whom the blood sugar fell to 17 mg. per cent. After intravenous dextrose the blood sugar rose to 218 mg. per 100 c.c. of blood, but later fell to 30 and 50 mg. **Thyroxin** was given, after which the blood sugar became normal. This patient also had chronic nephritis and died in uremic coma 14 days later. The autopsy showed complete destruction of the hypophysis. Since the hypophysis and thyroid are synergistic, it is possible that the hypophysis may have been a factor in this case.

Abrams and Gilligan, in studying the carbohydrate metabolism in human *hypothyroidism* induced by total ablation of the thyroid gland, found that it was

not significantly influenced except when derangements of carbohydrate metabolism were evident. Prior to the operations they found that the signs and symptoms of mild hyperinsulinism were manifest in patients with hypothyroidism, at the same level in blood sugar as patients with normal basal metabolic rates. It seems probable from these studies that with normal functioning insulin apparatus hypoglycemia is not so apt to result as when hyperinsulinism existed prior to the operation.

Womack expresses the opinion that at times it may be necessary for the body to utilize the secretion of the thyroid gland in hypoglycemia to maintain blood sugar homeostasis. Womack reports a very interesting case with the anomalous condition of a *goiter* and *hyperthyroidism*, associated with very low blood sugar readings and *hypoglycemic symptoms*. Since the hypoglycemic symptoms were serious and of the greatest importance, Womack suspected an islet cell adenoma and operated upon the patient. A normal appearing pancreas was found and a **subtotal pancreatectomy** was performed, following which the thyroid decreased in size to normal, the symptoms of hyperthyroidism subsided, and the patient's basal metabolic rate became normal after the operation. In other words, Womack felt, and the results in the case seemed to prove, that the hyperthyroidism was compensatory in an effort to release the glycogen stores from the liver to raise blood sugar levels, in spite of the hyperinsulinism.

Womack mentions a case of L. F. Aitken in which compensatory hyperactivity of the thyroid was associated with *hypoglycemia*. In this patient, amnesia, automatism, confusion, and unconsciousness occurred before breakfast. Several months later she had characteristic clinical picture of *Graves' disease*, her basal metabolic rate having been

plus 80 per cent. With the appearance of hyperthyroidism the symptoms referable to hypoglycemia became lessened. A subtotal thyroidectomy was done, following which the hypoglycemic symptoms increased in severity. Exploration of the pancreas showed a beta cell **adenoma**, the **removal** of which restored normal carbohydrate metabolism. Later, the patient developed evidences of *hypothyroidism* and is now being given  $1\frac{1}{2}$  to 2 grains (0.1 to 0.13 Gm.) of desiccated **thyroid** daily.

Womack cites Burns and Marx as having noted in studying the relation of the thyroid gland to the action of insulin, that "the presence of large amounts of thyroid hormone in the circulation enables the organism to prevent the occurrence of severe hypoglycemia in spite of the injection of relatively large doses of insulin. However, when the liver had been depleted completely of available glycogen the thyroid hormone did not prevent the hypoglycemia."

In Goldzieher's (*loc cit.*) study of 112 cases of chronic *hypoglycemia* 20 patients presented evidences of *hypothyroidism*. Many other cases of spontaneous hypoglycemia in hypothyroidism patients have been reported, so it would seem advisable to make routine blood sugar studies on all patients whose basal metabolic rate is below normal.

**Suprarenal Hyperinsulinism.**—Adrenin (epinephrine or adrenalin), the internal secretion of the medullary portion of the suprarenal glands, transforms liver glycogen and, to a less extent, muscle glycogen, into dextrose, which is immediately mobilized in the blood. It is apparent that when there is a deficiency in the secretion of the suprarenal glands, antagonistic to insulin secretion, there must be hypoglycemia.

Cannon, in his chapter on "Homeostasis of Blood Sugar" in his admirable

book on "The Wisdom of the Body," shows that when the vagoinsular system is in the ascendancy and the sympathoadrenal function is depressed, hypoglycemia results. Cannon also calls attention to the fact that the symptoms of hypoglycemia are identical with those symptoms resulting from an overdose of adrenalin. He further states that the mechanism of convulsions in severe hypoglycemia is the spontaneous introduction into the circulation of a large amount of adrenalin, which causes the convulsion that releases muscle glycogen and raises blood sugar. This explains why it is that the hypoglycemic patient, following a convulsion, may have a normal or even elevated blood sugar.

Turner reports a case of *Addison's disease* in which there were clinical evidences of medullary as well as cortical involvement of the adrenals. He expressed the opinion that the increased sugar tolerance in Addison's disease is associated with "relative hyperinsulinism, resulting from degenerative processes interfering with normal adrenal production."

Eiselberg, of Vienna, in an article on *nutritive allergic symptoms* in spontaneous hypoglycemia, reports that a number of his allergics have had varying symptoms of hypoglycemia. One case, a woman age 39, had suffered from headaches for several years. She also had dull pains in the upper right quadrant, with cramps coming on about 3 hours after meals. These symptoms disappeared after the use of rye bread, tea or cocoa, to which she was not allergic, but the pains recurred following the use of other foods to which she was sensitive. She suffered from fatigue, vertigo, tremors and her blood sugar readings were low. Eggs and zweiback, to which she was sensitive, would bring on the attacks with hypoglycemia almost at any time.

Another case reported by Eiselberg was an allergic woman who had amenorrhœa and spontaneous hypoglycemia, with a blood sugar reading of 59 mg. per cent. Her symptoms were ameliorated by regulating her diet.

**Hepatogenous Hypoglycemia.** — It is a well known fact that *spontaneous hypoglycemia* may be a sequence of massive infiltration of the liver by carcinomas and other tumors. It may result from the use of hepatoxins, as arsephenamine, phenylhydrazine, synthaline, phosphorus, mushrooms and other toxins that have a predilection for the liver. A number of tumors, severe grades of chronic hepatitis, congenital malformation of the liver, and other massive lesions of the liver, have been reported in cases associated with hypoglycemia. Cammidge is of the opinion that functional disorders of the liver, by interfering with glycogenesis, were factors in most of the 200 cases of spontaneous hypoglycemia which he reported in 1922. Best is also impressed with the relation of the liver to hypoglycemia. Unquestionably, anything that interferes with glycogenesis, that prevents the release of glycogen from the liver, or that exhausts the stores of glycogen in the liver, will be followed by hypoglycemia.

Mann and Bollman, in 1933, studying the effect of insulin following total removal of the pancreas and liver, found that insulin produced the same precipitated decrease in blood sugar level after the removal of the liver as in the normal animal in which the liver had been removed. From this observation they conclude that the liver is not essential for the hypoglycemic function of insulin. They first removed the pancreas of dogs, and 3 or 4 days later removed the liver. Determinations of the blood sugars were made before the removal of the liver and at half-hour intervals subsequently. Two or 3 hours after the removal of the

liver, when the blood sugar was still high, they gave large doses of insulin intravenously to the animals and the blood sugar rate was determined at half-hour intervals. The increased rate of sugar disappearance from the circulation after the administration of insulin was so great that they conclude: "There can be no question that the liver is not essential for the hypoglycemia action of insulin." It would seem that with decreased glycogenesis or decreased utilization of glycogen and a normal functioning pancreas, hypoglycemia would result from a relative excess of insulin.

A number of cases of chronic *hypoglycemia in childhood*, have been reported in which there were undoubted evidences of hepatic disease that could account for the hypoglycemia. Kramer (Jr. *Pediat.* 5:291 (Sept.) 1934) reports such a case—an infant 6 months old with poor appetite, weakness, fainting spells and generalized convulsions. The blood sugar was 18 mg. per 100 c.c. of blood. The convulsions persisted and later the blood sugar was 8.3 mg. per 100 c.c. of blood and a spinal fluid blood sugar was 11.3 mg. The autopsy showed a very large liver in which no normal liver cells were found. The pancreas appeared normal.

**Pancreatic Hyperinsulinism.** — In the majority of reported cases of *spontaneous hypoglycemia* the cause lies in an actual excessive secretion of insulin by the islet cells of the pancreas.

The recently recognized disease entity, *hyperinsulinism*, is being diagnosed with increasing frequency. Cases have been reported in practically every country in the world in which medical journals are published. It is interesting to observe the influence of American literature on clinical practice in foreign countries, and it is pleasing to note that in nearly all the articles on hyperinsulinism and spontaneous hypoglycemia in

foreign journals the authors have been generous in their references to contributions on the subject by American physicians. So many valuable contributions on hyperinsulinism and spontaneous hypoglycemia of pancreatic origin have been made to medical literature that it is not possible to mention even the names of the clinicians who have been pioneers in this new field of medicine.

While the nomenclature of disease is not essential in clinical studies, it seems advisable to consider the terminology in the diagnosis of hyperinsulinism and spontaneous hypoglycemia. Most of the cases reported have been called by the authors reporting them hyperinsulinism, though the terms "spontaneous hypoglycemia" and "chronic hypoglycemia" are also used. *Hyperglycemia* is a condition of the blood, not a disease entity, sometimes secondary to many endocrine disorders that result in actual or relative decrease in the secretion of insulin (hypoinsulinism). No one would think of reporting a case of diabetes as hyperglycemia. *Hypoglycemia* is also a condition of the blood, not a disease entity, resulting from and secondary to many disorders of metabolism, that may cause actual or relative excessive secretion of insulin (hyperinsulinism).

Since the term hypoglycemia does not identify the organ or organs that cause the disturbances of metabolism resulting in actual or relative excessive secretion of insulin, its use is not acceptable in diagnostic terminology as outlined in the book prepared by the committee on "Standard. Classified Nomenclature of Disease."

From the accumulated data in reports of several hundred cases of hyperinsu-

linism and chronic hypoglycemia, it may be assumed that in any case in which hypoglycemic symptoms appear, unless there are evidences of diseases of the pituitary, thyroid, adrenals or liver, hyperinsulinism is being dealt with. When the pituitary, thyroids or the suprarenals are the primary organs involved in the production of hyperinsulinism, it would seem that, according to scientific nomenclature, the diagnosis should be recorded as pituitary hyperinsulinism, thyroid hyperinsulinism and suprarenal hyperinsulinism. When primary disease or disorder of the liver is considered as the cause of hypoglycemia, with an assumed normal pancreas, relative hyperinsulinism is perhaps a factor in the hypoglycemia. However, in such cases it would seem advisable in recording a diagnosis, to name the primary disease of the liver with hypoglycemia as a secondary condition.

The question of nomenclature is not of material consequence. It is important, however, for the physician, whatever specialty he may practice, to know that hyperinsulinism, or spontaneous hypoglycemia, is a common disorder or disease, relatively more frequent than the opposite condition, diabetes mellitus (hypoinsulinism). The general practitioner, particularly, should familiarize himself with the wide variety of symptoms that occur in hyperinsulinism, because by recognizing the disease, he may prescribe the diet that will relieve many patients who otherwise would be dissatisfied with his services and pass on, unrelieved, into the hands of other physicians.

## OBESITY

By JOSEPH T. BEARDWOOD, JR., A.B., M.D.

**Etiological Factors.**—There is considerable dispute as to the exact rôle that the *endocrine glands* might play in any given case of obesity. It is obvious that thyroid deficiency and basophilism are accompanied by obesity but up to the present time the only glandular product which is of any marked value in the treatment of obesity is thyroid. While the other products may produce marked relief from the symptoms of glandular deficiency by themselves, they seldom cause a weight loss. Then, too, there are many cases of endocrinopathy which are not attended by obesity.

It has been maintained by many investigators that there must be other factors involved in the vast majority of cases. E. Spriggs, A. J. Leigh, H. Gardiner-Hall and D. Hunter (Proc. Roy. Soc. Med. 29:411 (Mar.) 1936) point out that in 60 to 75 per cent. of their cases they were able to obtain a family history of obesity. They believe that the true exogenous obesity is rare, *i. e.*, obesity resulting from a storage of excessive food intake because of inadequate exercise in a person whose metabolism is normal. It can be seen that bakers, cooks and those who indulge in alcohol might well have a marked difference between their energy intake and output.

The physiological problem of weight they believe to be due to appetite and activity which is definitely bound up with some internal mechanism due to the chromosomal constitution of the individual. They postulate that hormonal influences are responsible for the peculiar response to excess food and its utilization, and that the abnormality is due to overactivity on the anabolic rather than the katabolic side of the picture, and that, as a result, there is this storage of

excessive food in the form of fat which is quite independent of other oxidation processes of the body.

G. Booth and J. M. Strang (Arch. Int. Med. 57:533 (Mar.) 1936) report the results of investigations of blood-pressure and surface temperature determined after a meal of meat designed to attain satiety in 19 normal and 14 obese individuals. The response of the blood-pressure was identical in the two groups and possibly due solely to the work of eating. In the group of normal weight there was an elevation of the temperature of the skin beginning shortly after the start of the meal and reaching a maximum of 2° C. in 60 minutes. The elevation of the skin temperature in the obese group was definitely diminished, and delayed as compared with that of the group of normal weight. This difference and reaction may be one factor in the delayed sensation of satiety in obese persons and therefore a controlling factor in the determination of the large intake of these individuals.

**Treatment.**—The most recent review of this subject is that of J. J. Short and H. J. Johnson (J. A. M. A. 106:1776 (May 23) 1936) who feel that it is more important to determine the total metabolism than the basal metabolism. The latter is considered as the heat production per unit of body surface per unit of time, while the total metabolism is the heat production of the organism as a whole per unit of time—both of these measurements being taken at complete rest. These investigators performed an ingenious experiment to show the low energy production of the fat: a long needle with a thermocouple at the point was introduced through a thick layer of fat in the gluteal regions of obese individuals. The temperatures were re-

corded by means of an electrical recording apparatus. It was found that the lowest temperature was just beneath the skin, and that the temperature gradually rose as the muscle was approached. A sudden abrupt elevation to the usual body temperature was finally noted and was assumed to be at the point of entry of the thermocouple into the muscle.

These observers found a tendency to an increased basal metabolic rate which increased with the greater degrees of obesity, and they also found that the upper trend of metabolism is much more noticeable in the total heat production which averaged for all of their cases 22.5 per cent. above the normal.

It is evident from the foregoing that there is an increase in total metabolism in obesity. Since fat is comparatively inert, this increased heat production must be brought about by an increased activity of the muscle and gland tissue of the body. These are apparently stimulated to a higher rate of oxidation and an increase of heat and energy production. Other things being equal, the increase of heat production is directly proportional to the increase of surface area and, conversely, a reduction in weight brings about a reduction of total metabolism in direct proportion to the reduction of surface area.

Since in obesity there is already an increased total metabolism, the giving of metabolic stimulants in the form either of thyroid preparations or drugs such as dinitrophenol is entirely illogical. Short and Johnson have found that even small doses of thyroid extract have been followed by evidence of thyroid intoxication, and they believe that thyroid should only be used in those cases which show a drop in the basal metabolic rate after being placed on a proper dietary régime.

**DINITROPHENOL.**—*Untoward Effects.*—Following the introduction of dinitrophenol as a metabolic stimulant by

W. C. Cutting, H. G. Mehrtens and M. L. Tainter in 1933, there was a wide use of this drug—not only by the profession, but also in the form of many popularly-advertised reducing remedies. It would seem of some interest, in view of the many untoward effects and unfortunate complications of its use, to briefly review the toxic symptoms that might follow its use. Certain individuals are undoubtedly more hypersensitive to this drug than others, but attempts to determine in advance individual sensitivity have been for the most part unsatisfactory, according to G. M. Frumess and E. Matzger.

The earliest *toxic reactions* from dinitrophenol are headache, mild chest pains, backache, excessive sweating, feeling of warmth, night sweats, lassitude, nervousness, tachycardia, palpitation, lowering of blood-pressure; as the toxicity increases the following may result: vertigo, pharyngitis, otitis media, abdominal pain, derangement of taste, toxic hepatitis with jaundice, maculopapular erythema, urticaria, edema, purpura, extreme itching, delirium, high temperature and death.

J. M. Hitch and W. F. Schwartz (J. A. M. A. 106:2130. (June 20) 1936) present a very complete review of the unfavorable reports following the use of this drug. There have been 7 fatalities reported from dinitrophenol and 1 from dinitrocresol—2 of these were due to overdosage; 4 occurred in patients taking a dosage within the therapeutic range and possibly represent an allergic response; the remaining 2 died as a result of a complicating agranulocytosis. Thirty cases of polyneuritis have been recorded; 14 cases of rapidly developing cataracts, varying in time from 3 to 18 months after taking the drug. The smallest amount taken was 135 grains (4.5 Gm.), the largest 1900 grains (63.3 Gm.), the average dose being 870 grains (29 Gm.). These authors feel

that too little emphasis has been placed upon the cardio-toxic effect of dinitrophenol, and state that electrocardiographic changes, mostly alterations in the T-waves, have been reported as occurring as soon as 2 weeks after the drug was started, and lasting up to 10 weeks after its discontinuance. They also report a case of extensive exfoliative dermatitis in which practically all of the skin of the body was involved and which had lasted at the time of the report 10½ months.

It would seem, in view of the many adverse reports and the multiplicity of complications that may result, that dinitrophenol is a drug which should not be used except under the most carefully regulated conditions, and then only with a full realization of the many untoward effects that may be encountered.

EXERCISE.—The value of exercise as an adjunct in the treatment of obesity has been the subject of considerable differences of opinion. While most writers are in accord that proper exercise will aid in weight reduction, strenuous exercise seems to be contraindicated in many obese individuals because of the condition of the cardiovascular system. Then, too, exercise to be of much value must be indulged in regularly, and this presents a very practical problem to those who are unable to indulge in regular out-door exercise. The usual calisthenics suggested for aid in reduction are probably of little practical value in the first place and in the second must be performed in the privacy of the boudoir. It is of interest to read the suggestions of A. H. Douthwaite (*Brit. M. J.* 2:344

(Aug. 15) 1936), who points out that fat rarely accumulates over a muscle which is exercised regularly, and that most of the usual exercises prescribed for obesity neglect altogether the abdominal muscles, which must be kept in good condition in order to avoid the characteristic sag and pot-bellied appearance. He believes that any set of exercises should be of such character that they could be indulged in the home or office at frequent intervals through the day without causing any undue comment from others, and he suggests the following unique group of procedures:

1. Contract and expand the abdominal muscles while sitting or standing. This causes development of the recti and some extent the oblique.

2. Exercise the oblique and quadratus lumborum by standing and drawing the hips and lower ribs together first on one side and then on the other. This exercise can also be done in the sitting position after practice. Douthwaite suggests placing the finger tips over the muscles to be exercised as a means of educating the patient concerning the different muscle groups.

3. The pelvic floor can be strengthened by alternately drawing up and relaxing the anus. This apparently will prevent relaxed perineum so often present in fat people, and which may be a factor in constipation, hemorrhoids, and urinary incontinence.

4. The back should be developed to avoid poor posture. The head and body should be carried erect, and the lower abdominal muscles held tight.

While these exercises may seem a bit fantastic, according to the author they are helpful if done regularly enough to become a habit, and most of them have the advantage that they can be carried on from time to time during the day regardless of the patient's other activities.

## DISEASES OF THE RESPIRATORY TRACT

By FRANK WALTON BURGE, M.D.

**AMEBIASIS, PLEUROPULMONARY.**—Pleuropulmonary complications of amebiasis occur much more frequently than is generally supposed, according to A. Ochsner and M. DeBakey (J. Thoracic Surg. 5:225 (Feb.) 1936). They were observed in 15.8 per cent. of 2490 reported and in 15.7 per cent. of the authors' 95 consecutive cases of amebic hepatic abscess.

The greatest number (38 per cent.) of the patients in the collected series were in their thirties while the greatest number (40 per cent.) of the authors' series were in their fifties.

There were more males than females involved; 96.2 per cent. in the collected series and 93.3 per cent. in the authors' series. Also, in the authors' series, 9 patients were white and 6 colored.

Usually, pleuropulmonary complications of amebiasis are caused by an extension of an amebic hepatic abscess. Perforation of the abscess usually occurs into the lung or bronchus and rarely into the free pleural space. Very rarely, hematogenous pulmonary amebic abscesses may occur.

Pleuropulmonary amebic infections are classified into 5 groups, depending upon the type of pleuropulmonary involvement:

1. Hematogenous pulmonary abscess without liver involvement.
2. Hematogenous pulmonary abscess and independent liver abscess.
3. Pulmonary abscess extending from liver abscess.
4. Bronchohepatic fistula with little pulmonary involvement.
5. Empyema extending from liver abscess.

In the collected series, 14.3 per cent. were group 1 infections, 10.4 per cent. group 2 infections, 37.2 per cent. were

group 3 infections, 19.6 per cent. were group 4 infections, and 17.6 per cent. were group 5 infections. In a group of 15 cases, 46.6 per cent. were group 3 infections, 20 per cent. were group 4 infections, and 33.3 per cent. were group 5 infections.

**Diagnosis.**—Clinical signs of pleuropulmonary amebiasis are chiefly: cough, expectoration, fever, diarrhea, enlarged and tender liver, pain in chest, and cachexia. In the collected series, cough and expectoration were present in 92.5 per cent. of the cases, fever in 43.2 per cent., a history of a previous diarrhea was obtained in 41 per cent., diarrhea was present in 33.5 per cent., enlarged liver was present in 39.7 per cent., and chest pain in 31.3 per cent. The expectoration of chocolate-sauce pus is indicative of a communication between a liver abscess and a bronchus and is of diagnostic importance. Pulmonary signs are consolidation and cavitation. Moderate leukocytosis without concomitant increase in the number of polymorphonuclears is present. Marked leukocytosis indicates a secondary infection.

X-ray examination shows elevation and immobility of the diaphragm and a shadow at the right base, particularly in cases where a pulmonary abscess extends from a liver abscess. The shadow is triangular, with the base below and the apex above.

The diagnosis is made on the basis of the chocolate-sauce pus and the presence of amebas in the sputum and aspirated material.

**Prognosis.**—This is dependent upon the type of infection and the therapy employed, but probably more upon the latter.

In the collected series of cases the mortality in the various groups was:



group 2, 81.2 per cent.; group 5, 77.7 per cent.; group 3, 43.2 per cent.; group 4, 10 per cent.; group 1, 4.5 per cent. Cases treated with open drainage only, showed the highest mortality, 48.2 per cent. Cases treated with emetine only, showed the lowest mortality, 5.4 per cent. Cases treated with both emetine and open drainage, showed a mortality of 16.6 per cent. Total mortality in the collected series was 41.1 per cent.

Of the cases in the collected series treated without emetine, 43.9 per cent. recovered; while 91.8 per cent. of those cases treated with emetine recovered. Of the authors' series, 40 per cent. of those treated without emetine recovered, and 100 per cent. of those treated with emetine recovered.

**Treatment.**—The treatment of pleuropulmonary amebiasis consists of the administration of **emetine** and **aspiration of abscesses** that are not sufficiently evacuated through the bronchus. **Open drainage** is only done in cases of *secondary infection*.

**BRONCHOMYCOSIS.**—R. Fawcitt (Brit. J. Radiol. 9:172 (Mar.) 1936) describes a lung condition occurring in the farming communities of South Cumberland, the Lake District, and Westmoreland, which is attributed to the inhalation of a dust-borne fungus. For this condition the name "*bronchomycosis feniseicorum*" (bronchomycosis of haymakers and harvesters) has been coined.

There are said to be more than 100,000 identified species of fungi.

Castellani classified bronchomycoses as follows:

1. Those due to yeast-like fungi, *viz.*, fungi of the types monilia, cryptococcus, saccharomyces, blastomycoides, and endomyces.

2. Those due to filamentous fungi:
  - (a) fungi of the slender type, *viz.*,

nocardia, anæromyces, and vibriothrix; (b) those of a larger type, *viz.*, oidium and hemispora; and (c) those with typical fruitification, *viz.*, aspergillus, penicillium, mucor, rhizomucor, acremonia, sporotrichum, and acladium.

When the sputum is collected with due care to prevent outside contaminations and is examined at once, there are 3 possibilities:

1. The fungus, though present, is not virulent and not pathogenic, and lives saprophytically in the bronchi. When injected intravenously or directly into the lung of a rabbit, such fungus will produce no general or localized lesions.

2. The fungus is only a secondary invader. Under these circumstances intravenous inoculation of a rabbit with the fungus will cause death from a generalized fungus septicemia, but intrapulmonary inoculation will not produce any localized nodular lesions in the lungs.

3. The fungus is the primary cause of the bronchoalveolar condition. Under such conditions intrapulmonary inoculation of a rabbit will produce a characteristic nodular appearance of the lung and the animal will die spontaneously in from 15 to 21 days with both lungs infected. The nodules are usually about  $\frac{1}{8}$  inch in diameter. They may coalesce and become caseous. There is no intervening pneumonia, but some congestion, and the fungi and spores may be recovered from the nodules.

When these criteria are met in the absence of tubercle bacilli and the sputum yields fungi which are pathogenic to experimental animals, a diagnosis of bronchomycosis of the primary type may be made.

The condition simulates tuberculosis, being accompanied by a cough, mucopurulent sputum, cyanosis, frequent attacks of severe dyspnea on slight

exertion, patches of dullness and crepitation, râles, ronchi, and areas of increased vocal resonance.

The x-rays show a fine mottling throughout both lung fields except in the apices, which are clear, and a considerable amount of emphysema. These conditions are superseded by a generalized fibrosis as the condition improves or associated with fibrous rings walling off small cavities or surrounding calcified nodules.

There are 3 types of bronchomycoses: bronchoaspergillosis, bronchopenicilliosis, and bronchomucormycosis.

Seven cases of bronchomycosis are reported occurring in farmers. The symptoms of the disease developed rapidly during the movement of dusty, mouldy hay in a wet season when the hay was taken in when it was damp. In all the cases the histories and roentgenograms were similar. In 1 case coming to autopsy the silica content was normal, 0.15 per cent. In lung infections due to the inhalation of inorganic dusts, the onset of clinical symptoms and the spread of fibrosis are more gradual. The fibrosis becomes progressively worse. In lung affections due to organic dusts, probably fungus infections, the onset is more sudden and associated with more marked dyspnea, and the x-rays frequently show emphysematous bullæ and patches. Under treatment, recovery may take place with considerable fibrosis.

In bronchomycosis *feniseiorum*, the x-rays show evidence of an atypical bronchitis. The condition appears to be a definite entity. Its bronchomycotic nature is indicated by the following facts:

1. Fungi were isolated from the sputum.
2. Fungi (*aspergillus*, *penicillium*, and *mucor*) were isolated from hay.
3. In all of the cases mouldy hay was the supposed causative factor.

4. All of the recorded cases belonged to the farming class, *i. e.*, they were individuals whose daily life brought them into particularly close contact with fungi.

5. Postmortem appearance of the lung was similar to that described for fungoid conditions.

6. In most cases treatment with **potassium iodide**, a recognized fungicide, is curative.

**BRONCHOSPIROMETRY.**—In an attempt to separate the sputum from each lung in pulmonary tuberculosis, H. C. Jacobaeus (Brit. J. Tuberc. 30: 114 (July) 1936) injected with the aid of the bronchoscope different dye solutions into the bronchi of each lung and thus stained differently the sputum from each side. In a few instances differently stained sputum was obtained and then stained for tubercle bacilli and in one case sputum with tubercle bacilli was obtained from each lung. In cases with copious amounts of sputum no useful results were obtained.

Following this idea and with the hope that separating the air of one lung from the other bronchoscopically might be of value, at the suggestion of Professor Liljestrand a Pflüger's rubber cuff was applied around the distal end of the bronchoscope and the other end connected with an ordinary Krogh's spirometer in order to record the respiration. In this procedure (reported by Bjorkman and Frenckner) 2 bronchoscopes are used: one is introduced in one of the main bronchi, usually the left, because it runs for a longer distance without branching; the second bronchoscope ends in the trachea. Both ends of the bronchoscopes are surrounded by rubber cuffs that are inflatable, thus shutting off the air from each lung. The respired air is brought from the lung to the separate spirometers and the respiratory movements are recorded on

a kymograph, one lung above the other. In this way the respiratory movements are recorded simultaneously and are easily compared. During the procedure the CO<sub>2</sub> elimination is also determined.

The bronchoscopy is done under local anesthesia, using 2 per cent. percaïne solution. No pain is experienced but occasionally an uncomfortable sensation of suffocation is experienced by the patient. More than 150 tests have been made without accident other than an occasional slight temperature rise during the next few days.

The procedure has been done on normal as well as ill subjects and it has been found that the right lung is slightly more active in respiration, showing 53 to 56 per cent., while the left lung shows 44 to 47 per cent. Bjorkman experimented with patients in various positions in order to determine whether posture affected respiration. It has generally been assumed that the upper lobe would inflate more completely than the lower compressed lobe. However, the postural experiments revealed the opposite, both in regard to respiration and oxygen intake, the difference mounting to about 10 per cent. It is probable that due to the low blood-pressure in the pulmonary circulation, there is better circulation of blood through the lower lung. Also, it is possible that the diaphragm of the dependent part of the chest makes bigger excursions than in the upper part. This may be of some significance in pathological cases, since in diseases of one lung or the other it is of some importance on which side the patient lies.

Sometime during bronchospirometric tests, the subject coughs. Bjorkman has observed in both pathological and normal conditions that the coughing takes the form of sudden and powerful expirations, which under normal conditions are equally powerful in both lungs.

However, when one lung is diseased and the air content diminished, this is not the case. In one case of atelectasis of the lower right lung, the patient had a violent coughing attack during bronchospirometry and nothing was recorded on the graph from the diseased lung, indicating that the patient was only coughing with his sound lung. It is probable that there is no air behind that can be expired, and, in turn, expel the sputum. The nearer the residual air is to the respiratory position, the less chance there is of the patient coughing. This, no doubt, is the case with collapsed lungs. The lung that is in need of getting rid of its pathological secretions has greater difficulty in dispelling sputum by coughing the contents from the bronchi. Since learning this, it has been observed that a large number of unilateral lung cases have difficulty in dispelling sputum due to the affected lung being unable to cough. In some unilateral cases, the patient has been caught with a troublesome attack of coughing and the mucus has been heard rattling in the bronchi, but the attack ceased with no sputum having been brought up. In these instances it is possible that the sputum has been forced to return to the affected lung through the coughing from the sound lung. It is also possible that this difference in the ability of the lungs to cough serves as a protection against the spread of the infection to the healthy lung, from the infected lung.

### HEMOPNEUMOTHORAX, SPONTANEOUS. — *Etiology.* —

Analyzing a case of spontaneous hemothorax personally observed and also those reported in the literature, O. R. Jones and C. L. Gilbert (Am. Rev. Tuberc. 33:165 (Feb.) 1936) were impressed by the great similarity between the etiology of idiopathic pneu-

mothorax and hemopneumothorax. The factors appear to be the same so far as the rupture of the lung and the escape of the air into the pleural cavity are concerned, whereas the accompanying hemorrhage can be explained only on the basis of chance. When an emphysematous bleb ruptures because of increased intrapulmonary or intrathoracic pressure or by external forces, the usual occurrence is the escape of air into the pleural cavity. If in the course of this rupture a blood vessel is torn in the wall of the bleb or in the attached pleural adhesion, the escape of air is accompanied by a hemorrhage, the amount of which is determined by the size of the involved vessel and also by the various intrathoracic reactions resulting from the outpouring of air and blood into the pleural cavity. A case reported by Palmer and Taft demonstrates the part which chance plays in causing either a pneumothorax or a hemopneumothorax.

**Prognosis.**—In most cases the prognosis is good, but depends on the amount of the pleural hemorrhage.

**Treatment.**—In cases of *mild hemorrhage*, this should be **conservative**, whereas in patients suffering from *larger hemorrhages* the blood should be **removed from the pleural cavity and air replaced**. In some of the latter cases **surgical methods** may be used following the removal of blood.

**LUNG.—PULMONARY ABSCESS.**—**Etiology.**—C. L. Harrell (Virginia M. Monthly 63:134 (June) 1936) reported 7 cases of lung abscesses where 2 patients developed abscess following tonsillectomy under general anesthesia; in 4 instances it followed an operation on the stomach, the extraction of an infected tooth, pneumonia, and a very marked oral sepsis; while the cause in 1 case was undetermined.

**Treatment.**—C. L. Harrell (*Ibid.*) adds 7 cases of lung abscess to the 16 that he reported 4 years ago which were treated by **artificial pneumothorax**. Nine of the group were cured by this method alone, 1 patient died, while 3 came to operation, 2 of whom got well.

In producing pneumothorax of a tuberculous lung, an endeavor is made to collapse the lung completely and hold it at rest until it heals. In acute abscess or suppurative conditions of the lung, the objective is to promote and facilitate drainage, as it is through the process of drainage that pyogenic infections are thrown off and healing takes place. As soon as a diagnosis of lung abscess is made, small quantities of air should be injected in the pleural cavity to act as a buffer and prevent the lung from sticking. The wave-like motion through inspiration and expiration will continue and the lung will be in a better position to empty itself, and a larger percentage will recover in a shorter period of time. In the first series of 16 cases, the shortest period under treatment was 1 month, the longest was 6 months.

**Prognosis.**—In the second series of 7 cases, 1 patient died of cerebral abscess, although from all appearances the lung was healing satisfactorily. Two patients died while under treatment, one from pulmonary hemorrhage and the other from lack of coöperation. Both of these were chronic cases and were refused by the surgeon. One came to operation and recovered, the remaining 3 patients recovered, with an average of 3 months under collapse therapy.

Complete recovery occurred in 12 cases, or 52.1 per cent., under collapse therapy combined with rest, the highest percentage of recoveries given under any other form of treatment.

**Short wave therapy** was employed by E. Schliephake (Med. Klin. 32:380 (Mar. 20) 1936) in pulmonary abscess

caused by pneumonia, influenza, aspiration of suppurating material, embolism, suppurated echinococcus and bronchiectasis, when surgical treatment seemed inadvisable.

Wave-lengths of 6 and of 12 meters were used, depending on the etiology and the localization of the abscess. Occasionally treatments were begun with lesser energies and shorter durations and gradually both were increased—the durations up to 20 or 30 minutes. The intervals between the treatments as well as the total number differed in the individual cases. Patients received treatments every day, every second day, or twice each week.

Improvement was often noticeable after a few treatments, but the total number of treatments was sometimes 20 and even more than 30.

Others have used short wave therapy successfully in lung abscess. The apparatus must have great efficiency over a great air distance. The success of the treatment is dependent on the use of the proper technic. Liebesny was unsuccessful as long as he used apparatus with inadequate efficiency, but succeeded as soon as he employed a different apparatus with correct adjustment of the electrodes.

Reported results indicate that large suppurations may be absorbed under the influence of the short wave field. Fiandaca used it on 12 patients with gangrenous pulmonary abscesses.

This method of treatment does not tax the patient like a surgical intervention, and even patients with cardiac insufficiencies tolerate the treatment well. The general condition is frequently improved after the first treatment. The majority of cases heal without any undesirable sequels. In some cases, the subsequent x-ray examinations reveal a slight, diffuse, turbidity, but in many

cases later roentgenoscopy discloses nothing indicative of a former disorder.

**LUNG CYSTS.—*Diagnosis.***—J. D. Adamson (Canad. M. A. J. 35:1 (July) 1936) states that the clinical recognition of *congenital* cystic lung has become possible only since roentgenography and bronchoscopy have come into common use. Antemortem diagnosis has been made only within the past 10 years.

The condition has ceased to be a mere pathologic curiosity and has become a clinical entity of importance. It must be kept constantly in mind when making a differential diagnosis in chronic pulmonary disease of any sort. Interest is enhanced by the fact that almost any chronic condition of the lung may be simulated. Cases have been mistaken for and reported as chronic pneumothorax, chronic cavitating tuberculosis, chronic pleurisy with effusion, diaphragmatic hernia, chronic empyema, chronic abscess neoplasm, etc.

**PULMONARY HEMORRHAGE.—*Treatment.***—O. S. Kazarovskaya and V. I. Mordvinkina (Problemy Tuberk. No. 7:973, 1936) report 96 transfusions with blood plasma in 53 patients. Thirty-three of the patients had a persistent profuse bleeding which had resisted the various hemostatic measures, such as administration of calcium chloride, autohemotherapy and horse serum. The amount of blood plasma infused at one time amounted to from 20 to 40 c.c. Hemorrhage was arrested after 1 transfusion in 31 cases, after 2 in 9 cases, and after 3 in 11 cases. The method failed in 2 instances. It was effective in 96 per cent.

The plasma was secured from the Leningrad Institute for Blood Transfusion. It is prepared from donors of groups A and B. It does not contain agglutinins and can be given without regard for the blood group of the recipient. It does not produce anaphylactic

reactions on repeated injections. It differs from serum in that it does not contain fibrinogen.

The advantage of this method is that only a small dose is required, the action is rapid, there are only a few general reactions, and there is a total absence of a focal reaction. Infusion of blood plasma has the effect of increasing blood coagulability, the lowering of which constitutes one of the most important factors in the complicated mechanism of pulmonary hemorrhage.

**PULMONARY SEQUESTRUMS.**—*Pathogenesis.*—A. Bertelsen (Hospitalstid. 79:474 (May 5) 1936) emphasizes that age is a factor in the pathogenesis of pulmonary sequestrums. In 14 of the 18 cases found in the literature in which the age was specified, 11 belonged in the older age group and 3 patients were between the ages of 5 and 11. The tendency to thrombosis, possibly due to weakness, is an important factor in some instances; in others, the cause may be loosening of lung tissue in closely located pulmonary abscesses.

*Symptoms.*—The start is usually a fibrinous pneumonia without crisis, constant high fever and continued pulmonary symptoms, indicating a local complication. Symptoms of local abscesses may appear and more often empyema may develop.

*Diagnosis.*—Diagnosis may not be made until after death. After thoracotomy, spontaneous expulsion of the sequestrum may lead to a diagnosis. The course of the patient's condition may suggest the complication, in which case an attempt should be made to verify the diagnosis by x-ray examination, which may sometimes reveal a sequestrum.

*Prognosis.*—This is grave. Of the 18 reported cases, 14 were fatal; in 2 of the cases with recovery the seques-

trum was removed spontaneously through a thoracotomy, and in 2 by operation.

### MAGGOT AND ALLANTOIN THERAPY.

—Seven cases, in addition to the one previously recorded, of maggot therapy in *suppurative lesions of the lung and pleura*, are reported by N. Bethune (J. Thoracic Surg. 5:322 (Feb.) 1936) as well as 1 case treated by allantoin alone. Three were cases of *tuberculous empyema with bronchopleural, pleurocutaneous fistula*. One of these 3 cases was cured following thoracoplasty, 1 is permanently improved and awaiting thoracoplasty, and 1 died of contralateral disease after having shown temporary local improvement. One patient, with *tuberculous osteomyelitis with bronchocutaneous fistula* showed temporary local improvement and died of disseminated disease. One patient with *recurrent nontuberculous empyema* was cured. One patient with *gangrene of the lung* showed temporary improvement, and died of pulmonary hemorrhage not connected with the specific therapy. One patient with an *abscess of the lung* was cured. One patient with *tuberculous empyema* was treated with allantoin irrigations but did not improve and died.

Out of a total of 8 cases treated with maggots, 4 were cured, 1 was permanently improved, and 3 were temporarily improved followed by death. In one of the cured cases, it is possible that the maggots played only a minor rôle in the cure. In none of the deaths were the maggots even remotely responsible.

Maggots will not venture into deep narrow sinus tracts; they are surface feeders. The wound must be wide open, so that maggots are not suitable for small openings into the lung or pleura.

Their natural food is bacterial-laden pus. They eat only dead cells; the

fouler, the better. They cause no hemorrhage, and do not disturb any living tissue. They will not live in healthy granulating tissue. Their presence in wounds is tolerated only for a comparatively short period of time. Possibly an antimaggot substance is produced in these wounds.

Maggots will ingest living tubercle bacilli and the bacilli are easily found in the gut of the larvæ. Apparently, the maggots suck them in with the free floating pus, or easily detachable dead cells. The number of bacilli found in the wound on direct smear decreases and suggests that the bacilli are not just excreted back into the wound by the maggot. Exactly what happens to the bacilli in the gut of the maggot is not yet known.

Maggots are difficult to handle and can be a great nuisance in chest cases. They are comparatively fragile organisms, and are difficult to breed unless they are given great care and attention and special apparatus is used. They must be used at the proper period of their life cycle. Their life is short. Although rubber, adhesive tape, liquid cement, collodion, Unna's paste, calamine lotion, and Friar's balsam was used as a cage, none of them were really satisfactory in confining them to the wound. A superior covering of the cage was made from pieces of transparent, washed x-ray films, perforated for air, with a needle. This was found to be better than Baer's wire gauze netting, as the transparency gives a clear view of the wound.

Maggots gave good results in extrapulmonary, but intrathoracic, lesions, such as mixed infection tuberculous empyema with bronchopleural fistula, and nontuberculous foul empyema. When used prior to a thoracoplasty, the comparatively clean pleuras resulting

from their use adhered more easily than those grossly infected.

In intrapulmonary lesions, such as gangrene or abscess, unless the cavity is laid wide open, their use is not advocated.

W. Robinson (J. Bone and Joint Surg. 17:267 (Apr.) 1935) discovered allantoin to be one of the natural excretions of the maggots and suggested its use in wounds.

N. Bethune (*loc. cit.*) stated that a saturated aqueous solution (0.5 per cent.) seems to possess no bactericidal efficiency. It will not kill tubercle bacilli, staphylococci, or streptococci. However, it seems harmless to the tissues.

Allantoin seems to reduce the coagulation time of the blood. This may be the reason why maggots have not been the cause of hemorrhage in wounds. Of 4 cases observed, the coagulation time of the patients' blood fell in 3 and was unchanged in 1 after maggot implantation.

The blood coagulation time fell in 2 cases and remained unchanged in 2, when mixed with the wound discharges before and after maggots had been used. In 1 case the blood coagulation time fell when it was mixed with pus after allantoin irrigations as a check.

*In vitro*, the same fall after allantoin was added to blood, was noted. For example:

|  |           |
|--|-----------|
| Coagulation time of whole blood..  | 7.0 min.  |
| Coagulation time of blood and distilled water (5 c.c. plus 0.5 c.c.)                           | 7.45 min. |
| Coagulation time of blood plus 0.5 per cent. allantoin aqueous solution (5 c.c. plus 0.5 c.c.) | 5.15 min. |
| Coagulation time of blood plus 0.5 per cent. calcium chloride in distilled water               | 6.0 min.  |

In contrast to the above is an experiment in which 10 gm. (2½ drams) of the crystalline allantoin was taken by mouth, on an empty stomach, and the coagulation time of the blood was checked hourly for the next 3 hours. No change

was noted. Also, 10 c.c. ( $2\frac{1}{2}$  drams) of a 0.5 per cent. aqueous solution of allantoin injected intravenously did not affect the coagulation time of the subject's blood. Unfortunately, the urinary content of allantoin was not checked following administration. However, it is rather suggestive that the coagulation time of the blood of pregnant women falls at the same time as there is an increase of allantoin in their urine, which must be derived from an increased concentration of allantoin in the blood. This, of course, may just be coincidence, resulting from other conditions.

Although it has not been tried, it may be possible to stop a generalized oozing from a wound by dusting onto the surface a finely ground-up powder of allantoin crystals.

### MEDIASTINUM.—TUMORS.

—*Treatment*.—P. Bull (Norsk mag. f. laegevidensk. 97:329 (Apr.) 1936) previously reported 2 cases of dermoid cyst in the anterior mediastinum in 1929 and one of fibromyxanthoma in 1931 in which operation was performed; the patients are living and well.

In the first case of microscopic diagnosis of *myxosarcoma*, the onset was sudden, with violent pain in the left side of the chest and the left arm and hemothorax. At the operation, in 1932, a soft tumor, the size of an orange, was excochleated from the posterior mediastinum. The patient is well.

In the second case, a *bronchogenic cyst*, there were sudden laryngospasms repeated almost daily for 2 months. **Transpleural extirpation** of the cyst was done. Death occurred from mediastinitis.

In the third instance, a solid tumor microscopically diagnosed as a *fibroblastic tumor* of moderate malignity was excised from the anterior mediastinum. **Thoracoplasty** was performed and

complete healing resulted. Nine months later hemoptysis occurred, and a cavity the size of a walnut appeared under the right clavicle. The operative intervention is believed to have revived an old disorder in the top of the lung.

In the last case of atypical *sarcoma* in the anterior mediastinum, probably from a neurofibroma, there had been paroxysmal coughing with vomiting and a sense of oppression and pain radiating to the neck. X-ray examination showed a tumor the size of an egg in the upper left side of the chest. Four months later, in January, 1935, the tumor had doubled in size. Preceded by **artificial pneumothorax, transpleural extirpation** was easily accomplished. The tumor was situated above the heart, was solid, and weighed 184 grams. In December, 1935, the patient was well and had been pregnant for 5 months.

Mediastinal tumors often set in suddenly and with rather unusual symptoms, and it may be difficult to determine before operation whether the tumor is malignant or benign. Roentgenography in several planes is necessary for localization of the tumor before operation. Artificial pneumothorax aids in making the roentgenogram clearer, and thoracoscopy is probably the best means for localizing the tumor and at the same time affording an idea of its nature.

**Rectal ether-oil narcosis** may be advantageous in these interventions.

**ARTIFICIAL PNEUMOMEDIASTINUM.**—Air, injected into the mediastinum, is used by L. Condorelli (Minerva med. 1:81 (Jan. 28) 1936) as a contrast medium for x-ray visualization of the mediastinal structures. The punctures are made as follows:

The patient is put in the dorsal position without any pillow, having his neck in extension. If the air is going to be injected in the anterior mediastinal cavity, the central point of the supra-



sternal fossa is compressed by the surgeon with the index finger of the left hand and a needle, 10 cm. long and bent at an angle of  $120^\circ$  4 cm. from its point, is introduced to a depth of from 2.5 to 3.5 cm. and then inclined so that the point of the needle follows the posterior aspect of the manubrium steri, which is the anterior boundary of the cavity. Aspiration through the needle, temporarily connected to a sterile syringe, is performed to avoid insufflation into a blood vessel. The pain caused by the puncture is slight and no accidents follow.

If the air is to be injected into the posterior mediastinal cavity, the needle is introduced at the center of the middle line of the neck, at a point 2 finger-breadths above the fossa suprasternalis, as if for a tracheal puncture. When the point of the needle reaches the anterior wall of the trachea, the needle is inclined downward, tangentially to the trachea to a point 2 cm. below the suprasternal fossa. At this point the air insufflation can be performed.

As a preliminary work for the establishment of the aforementioned technic, injections of two different colored liquids into the mediastinum of cadavers were made, and it was found that there is an anatomic septum separating the mediastinal anterior and posterior cavities, which is formed by the deep layers of the middle cervical fascia and the posterior aspect of the pericardium, in front and by the mediastinal pleuræ at the sides.

The boundaries of the mediastinal cavities and the routes through which the colored liquids disseminate themselves after the injection were verified. The verifications clarify the significance of the x-ray shadows of the mediastinal structures in artificial pneumomediastinum and the mechanism of expansion of the air injected. Artificial pneumo-

mediastinum is of importance in the x-ray examination of the mediastinum for the diagnosis of pleuromediastinal diseases.

**PLEURA.—TUMOR.—*Diagnosis.***—W. Bromme, H. P. Nelson and T. Findley, Jr. (Am. J. Cancer 24: 334 (June) 1935) report a case in which death occurred from osteosarcomatous metastases to the pleura, 13 years after the appearance of the primary lesion, illustrating the diagnostic value of artificial pneumothorax. In this case, the biopsy specimens, taken more than 10 years apart from the two sites, show that in occasional instances the human organism may harbor sarcoma for a time considerably beyond the usual experience. Unawareness of this fact may, as in the case reported, lead to diagnostic uncertainty. Under these circumstances, direct confirmation becomes essential and diagnostic pneumothorax is a valuable aid in the study of pleural effusions of doubtful etiology. It should be carried to the point where complete visualization of the pleural surfaces is possible.

It may be that diagnostic pneumothorax is more widespread than the current literature would indicate. However, it is felt worth while to emphasize its special applicability to lesions of the lung and pleura masked by effusion. If the films are taken while the patient lies on his sound side, residual fluid will not obscure the costophrenic angle and diaphragm in question.

Judging from the appearance of the visceral pleura and the readiness with which the lung collapsed, it is possible that these metastases had not extended from the lung outward, as is usually the case in hematogenous spread.

**PNEUMONIA.—*Pathology.***—The blood sugar and the urinary chlorides in 23 cases of pneumonia were

studied by S. N. Sinelnikov, R. M. Perchik and O. N. Dorokhova (Klin. med. 13:1474 (Oct.) 1935), who reached the conclusion that pneumonia is a condition of a pathologic nondiabetic acidosis. Physicochemical alterations in the tissue colloids take place because of the upset in the acid-base balance in favor of acidosis, giving rise to alterations in the *carbohydrate and chloride metabolism*. It was found that the blood sugar in all the cases was raised above the normal (from 120 to 160 mg.) during the stage of hyperpyrexia and that these figures persisted until the crisis. There was a simultaneous sharp fall in the excretion of chlorides in the urine (from 0.58 to 1.3 mg. of sodium chloride in 24 hours), which persisted until the critical fall of the temperature. The amount of urine excreted during the stage of pyrexia averaged from 500 to 800 c.c. in 24 hours. Following the crisis, the blood sugar returned to normal, the urinary excretion rose, and with it the amount of excreted sodium chloride increased to reach the normal on about the eighteenth or twentieth day. The increase in the excreted sodium chloride was more marked than that of diuresis. The use of **insulin therapy** in the series resulted in lowering the mortality to almost zero. The chloride metabolism was rapidly restored to normal with the simultaneous lowering of the hyperglycemia.

**PNEUMOCOCCUS TYPE II PNEUMONIA.**—*Treatment.*—During 2 consecutive periods, of 3 years each, divergent clinical results were obtained by M. Finland and H. F. Dowling (Am. J. M. Sc. 191:658 (May) 1936) in the treatment of pneumococcus Type II pneumonia. During the period from November, 1929, through May, 1932, it was possible to demonstrate a considerable reduction in the mortality and rapid ame-

lioration of fever and symptoms in cases of Type II pneumococcus pneumonia treated with **specific antiserum**, as compared with contemporaneous and comparable nonserum treated cases due to the same type of pneumococcus. During this period, no deaths occurred among 29 patients under 40 years of age, who were treated with serum before the end of the fourth day of the disease, and no cases were encountered in which bacteremia first developed or extensions of the pulmonary lesions were first noted following treatment with the serum.

In the three succeeding years, from June, 1932, through May, 1935, the effect of serum treatment on the mortality was obviously less striking; clinical improvement was often delayed in the patients who did recover, and there were cases in which extension of the pulmonary lesions occurred, or in which bacteremia either developed or recurred following serum treatment.

The percentage of serum treated cases that died during the latter period was almost the same as among the non-serum treated cases. The difference in results could not be entirely due to the greater incidence of bacteremic cases in the later period, because the mortality among the patients with sterile blood cultures who were treated at this time was almost the same as among non-serum treated cases. Also, a number of deaths occurred among treated patients under 30 years of age. Nor could the differences be attributed to the inclusion of cases treated with serum late in the disease or while moribund. When all patients were excluded who had died within 24 hours after the first dose of serum, or who received less than 30 c.c. of serum before the end of the fifth day of the disease, the differences in the mortality were still great.

Attention was then directed to the *amount of serum* given. The average

total volume of serum per patient was only slightly less in 1932-1935 than in the preceding period. The total amount of antibody given each patient was calculated, as nearly as possible, on the basis of units consistent with a Type II antibody content of 200 units assigned to Felton's standard serum F 146, or 150 units for the National Institute of Health's standard serum P 11, and the average dose in standard units was determined. It appeared that the cases treated in the years 1932-1935 received, on the average, only 30 per cent. of the actual amount of Type II antibody given to Type II patients during the years 1929-1932.

**Treatment.**—The following tentative plan of dosage for Type II pneumococcus pneumonia cases is based upon observations on the effect of various amounts of antibody:

An amount of Type II antibody equivalent to 100,000 or, preferably, 150,000 units of the proposed standard serum, should be given to the patient in as short an interval as is consistent with the avoidance of untoward reactions, as soon as the diagnosis is made.

An additional 200,000 units should be given to all cases showing Type II pneumococci in the blood culture. This amount also should be given in as short an interval as is consistent with safety and even in spite of apparent improvement in the patient's condition.

Additional amounts of 50,000 to 100,000 units should be given at intervals of 6 to 12 hours in all cases until the fever and other acute symptoms are relieved, or until it is shown that these symptoms are not due to the Type II pneumococcus pneumonia.

After treatment is once begun, it is unwise to permit an interval of more than 12 hours to elapse without giving further serum, unless the patient is relieved of fever and serious symptoms.

Treatment with antibody beginning after the end of the fourth day of illness is probably of no benefit, except possibly in nonbacteremic cases, and then only if treatment is begun during the fifth day.

The results of blood cultures are the most important guide to serum dosage in addition to being of great prognostic significance.

The interests of physician and patient are best served if only serums of high potency in Type II antibody are released for treatment of patients with pneumonia due to this type.

**PNEUMOCOCCUS TYPE III PNEUMONIA.**—R. L. Cecil, N. Plummer and M. McCall (Am. J. M. Sc. 191:305 (Mar.) 1936) found that pneumococcus Type III ranks third as an exciting agent in lobar pneumonia, causing 11.8 per cent. of all pneumococcal pneumonias. It is surpassed only by pneumococcus Type I and Type II in respect to prevalence.

The incidence of pneumococcus Type III increases with age. In a series of 500 cases, Type III was responsible for 32.8 per cent. of all pneumococcal pneumonias that occurred after the age of 60.

Type III infection is relatively commoner in women than in men. The incidence rate for women is 18.2 per cent., as compared with 11.6 per cent. for men. This is in sharp contrast to Type I and Type II infections, where the incidence percentage for the two latter types is considerably higher for males than for females.

Pneumococcus Type III pneumonia is very prone to occur in individuals who are already the victim of some chronic disease. In the series of 500 cases, 49.9 per cent. of the patients were afflicted with some chronic malady. This association of chronic disease with pneumonia was much higher in Type III than in Type I or Type II infections.

Bacteremia was noted in 29.4 per cent. of the Type III patients who were subjected to blood cultures.

**Prognosis.**—The death rate for the series of 500 cases of Type III pneumonia was 42.2 per cent., a figure that agrees closely with that reported by others. In Bellevue Hospital, New York, however, Type III pneumonia ranks second in severity, being surpassed by pneumococcus Type II pneumonia, with a death rate of 48.8 per cent.

The death rate for Type III pneumonia was influenced by the patients' ages and the incidence of chronic systemic disease. In bacteremic cases the mortality was 85.4 per cent. In patients under 40 years, the death rate was approximately 20 per cent.; over 60 years it was 65.4 per cent. In patients without systemic disease, the death rate was 32.1 per cent.; with systemic disease the rate was 53.6 per cent.

**Treatment.**—There is no satisfactory serum therapy for pneumococcus Type III pneumonia at the present time. The most promising outlook with respect to a specific treatment is the **enzyme of Avery**, which destroys the specific carbohydrate in the capsule of pneumococcus Type III, and which, in the case of animals infected experimentally with lethal doses of Type III pneumococcus, has distinctly curative properties.

**PNEUMONOKONIOSIS (ASBESTOSIS).**—L. Martz states that asbestosis develops usually from 5 to 15 years after the beginning of the inhalation of asbestos dust.

A. J. Lanza, W. J. McConnell and J. W. Fehnel have made the following observations:

1. Prolonged exposure to asbestos dust caused a pulmonary fibrosis of a type different from silicosis and demonstrable on x-ray films. Clinically it

appears to be of a type milder than silicosis.

2. Cases of definite cardiac enlargement were frequently found to be associated with asbestosis.

3. A predisposition to tuberculosis due to asbestos dust was not indicated.

4. Asbestosis as observed in a series of cases had not resulted in marked disability in any case.

5. It is not known how much asbestosis may add to the mortality of pneumonia and acute nontuberculous pulmonary infections.

6. It is not practicable as yet to establish standards for the asbestos dust content of air.

7. The amount of dust in the air in the asbestos plants can be substantially reduced.

It is recommended:

1. That the industry seriously face the problem of dust control in asbestos plants.

2. That new employees be examined physically, including x-ray examination of the chest, and rejected for employment if they show tuberculosis or pneumokoniosis.

## **PNEUMOTHORAX, ARTIFICIAL. — Complications.**

W. A. Zavod (Am. Rev. Tuberc. 33: 48 (Jan.) 1936) states that 3 cases of fibrin bodies in the pleural space were reported prior to his report on a white male, age 44 years, a coal miner, who was ill since 1931. He was admitted to the Grasslands Hospital in Valhalla, N. Y., in July, 1932, and a diagnosis was made of far advanced productive pulmonary tuberculosis, involving the upper third of the right lung and the upper two-thirds of the left lung, with cavitation in the latter. The sputum was positive. Therapeutic pneumothorax was begun on the left side August, 1932. In April, 1933, his sputum was negative. Janu-

ary, 1934, fluid appeared in the left pleural space. The fluid contained 3,840 white cells, no red cells nor tubercle B., nor other organisms. August, 1934, the fluid disappeared and a mass was seen on the diaphragm and interpreted as a fibrin body. The patient died December, 1934, from tuberculous meningitis.

An autopsy showed the left lung collapsed 70 per cent. The parietal and diaphragmatic pleuræ were covered with a shaggy coat of fibrin. Three fibrin bodies were found in the pleural cavity; one was attached to the base of the lung, the other two were lying loosely on the diaphragm. They were ivory-colored, oval and flat in shape, resembling pebbles, and of lipomatous consistency, sinking in water. Section showed them to be homogeneous with lines suggesting laminæ.

Fibrin bodies are being observed more frequently as therapeutic pneumothorax cases increase. Fleischner was the first to describe a fibrin body that he saw on fluoroscopy. Their origin remains problematical. The two most popular theories are: (1) that fibrin bodies are formed by the agglomeration of fibrin in a pleural effusion and that no exudation of blood is necessary: (2) that they are of hemic origin and this theory is based on the fact that in a few cases there was clinical evidence of hemorrhage into the pleural space. Everyone agrees that fibrin bodies are of no clinical importance and that they disappear spontaneously and cause no ill-effects by their presence. They vary in size from that of a cherry to a lemon. Their resemblance in shape to that of a pebble has been explained by the rhythmic waves in the pleural cavity fluid which are brought about by cardiac impulse and respiratory movement.

The incidence of their occurrence in pneumothoraces is variously reported.

It is believed that the incidence is still higher because they are frequently overlooked or blotted out by the heart shadow. Their diagnosis is not difficult. Fluoroscopy and the x-rays show them as sharply outlined dense shadows. Infrequently a conglomeration of fibrin may resemble an adhesion. Pedunculated fibrin bodies have been reported.

**PULMONARY TUBERCULOSIS. — *Diagnosis.*** — In discussing the *mirror test*, R. C. Cohen and W. B. Wood (Brit. M. J. 2:65 (July 11) 1936) believe that the test should be done in the early morning when possible.

The patient and examiner sit as for ordinary indirect laryngoscopy, and a large size mirror, such as a No. 6, is held with its surface horizontally above the larynx. The patient is instructed to give several short barking coughs, and the mirror is thus sprayed with bronchial secretion. It is then withdrawn along the roof of the mouth, care being taken to avoid brushing its surface against the tongue. Flecks of yellowish secretion of pin-head size are characteristic, though not typical of tuberculous expectoration. Muroid or watery secretion usually, but not invariably, yields a negative result. The flat of the mirror is now applied to one end of a slide and drawn along it, leaving a thin film which is dried and stained in the usual manner. The possibility that the slide may be contaminated when the mirror has been used in a previous test is remote, but careful sterilization of the mirror is essential. It has been suggested that all-metal mirrors, now sometimes employed for indirect laryngoscopy, might be a useful safeguard.

By this method of examining secretion ejected directly from the lungs and collected by a mirror held over the larynx, tubercle bacilli may be demonstrated quickly and conveniently. The

test frequently enables the confirmation of a diagnosis of pulmonary tuberculosis suggested by history, symptoms, or physical signs, to be made without the delay that must occur when the patient is given a sputum outfit. Difficulties in securing the return of sputum flasks by mail are obviated. This advantage will be especially appreciated by those who work in country districts or among uncivilized communities. Malingering may be circumvented and the patient who consciously or unconsciously swallows his sputum may be induced to supply a sample of pulmonary expectoration by this means. Judging from a limited experience with this test, it is more delicate than the ordinary sputum test, and it may enable such accessory methods of examination as gastric lavage and bacterial investigation of the stools to be dispensed with. Though it is less delicate than the sputum concentration test, it can be used when no sputum is available for that purpose.

**Immunity.**—In a study of the acquired resistance to tuberculosis, R. S. Reichle and M. Gallavan (*Arch. Path.* 21:797 (June) 1936) observed 81 cases, 8 of primary tuberculous infection and 73 of reinfection. The patient who has a primary tuberculous infection usually dies not because of a pulmonary or intestinal lesion but as a result of hematogenous dissemination from that point. Negro patients in the series were a factor definitely tending to decrease the number of cases of lymphatic and hematic blockade. Thus, although 73.1 per cent. of the white patients belonged in the group in which a "lymphatic block was present," only 44.1 per cent. of the negroes were represented in this group. In the group in which a hematic block was present the negroes were represented by 58.5 per cent. and the white patients by 71.6 per cent. Almost half of the negroes (47 per cent.) had sub-

acute pulmonary tuberculosis, whereas almost half of the white patients (43.9 per cent.) had chronic fibrous pulmonary tuberculosis.

The type of disease is of distinct importance in the determination of lymphatic and hematic blockade, for the incidence of efficient lymphatic blockade rises from 30 per cent. in cases of sub-acute pulmonary tuberculosis to 90.9 per cent. in cases of chronic fibrous tuberculosis, the incidence of efficient hematic blockade being 45 and 77.2 per cent., respectively.

Reisner's observations that blockade against an extrapulmonary lesion is less efficient than that against a pulmonary lesion is perhaps suggestive that in 50 per cent. of the cases of extrapulmonary lesions there was a break in the lymphatic blockade, and in 75 per cent. a break in the hematic blockade. That chronic tuberculous disease of the lungs is rarely associated with the same condition in any other organ, however, is shown by the fact that in only 2 cases was there associated pulmonary and extrapulmonary disease. These results must be interpreted as a manifestation of resistance.

**Treatment.**—The segregation of patients with open incurable tuberculosis in special institutes is advised by Hanke (*Ztschr. f. Tuberk.* 74:248 (Jan.) 1936) in the interest of public welfare. The purpose and aim of the segregation of these patients is to remove these disseminators of bacilli from healthy persons and thereby prevent the further spreading of tuberculosis. Patients who have a cirrhotic productive form of tuberculosis, are free from fever, and are not bedridden, are suitable for residence in such an asylum. Patients with the exudative forms and with constant fever, however, should remain under hospital care. Among patients who were admitted to an institution for

segregation were some who were not incurable and who were amenable to surgical treatment. Some of these patients refused to submit to such treatment. Such cases must be impressed with the fact that they have obligations toward their families as well as toward the public, *i. e.*, toward those who have to bear the burden of their support. This responsibility toward their family and the public, whom they expose to the danger of infection, should be impressed also on patients with open tuberculosis who have been segregated for some time but who then demand to be discharged in order to return to their families.

In order to overcome the resistance of some of these patients, it might become necessary for the state to intervene by means of a law for the compulsory segregation of patients with open incurable tuberculosis.

**TREATMENT OF HEMOPTYSIS.**—K. Fang (Wien. med. Wchnschr. 86:571 (May 23) 1936) differentiates two types of tuberculous hemoptysis, the type that results from the rupture of a larger pulmonary vessel (*rhesis*) and that which takes place through the intact vascular wall (*diapedesis*).

*Rhesis* is frequently refractory to all therapeutic interventions and ends fatally, but in some instances **pneumothorax** treatment, **phrenicectomy**, or **thoracoplasty** may be helpful. In *diapedesis*, however, in which a disturbance in the coagulation of the blood plays a part, **hemostyptic remedies** are advisable.

As **parathyroid extract** produced favorable results in various types of hemorrhages, it was tried in the treatment of pulmonary hemorrhages of 102 tuberculous patients. The success of the treatment was complete in 81 cases, moderate in 8, doubtful in 9, and failed completely in 4 cases of *rhesis*. The usual mode of administration was by

intramuscular injection (rarely intravenously.) As a rule, 1 c.c. (16 minims) was given 3 or 4 times daily. The injections were usually continued for another day after the hemorrhage had ceased. They were always well tolerated.

**Surgical Treatment.**—**ARTIFICIAL PNEUMOTHORAX.**—The technic of artificial pneumothorax as recommended by F. W. Burge is as follows:

**Apparatus.**—Two glass bottles, capacity usually 2 liters each, graduated in 50 c.c., are connected together by rubber tubing and have valve adjustments for syphoning fluid from one bottle to the other.

A U tube water manometer measured off in 0.5 c.c. is connected to the tubing of the proximal bottle. The 0.5 c.c. marks are labeled as 1 c.c. by recommendation of the American Sanatorium Association Committee, 1935, so that the difference in the levels of water in the two arms of the U tube can be reported without multiplying by 2, as was done formerly by some workers.

**Sterilized:**

Rubber gloves.

Special metal three-way stopcock.

Rubber tubing: 10 inches of  $\frac{1}{8}$ -inch bore by  $\frac{1}{16}$ -inch wall, and 24 inches of  $\frac{3}{16}$ -inch bore by  $\frac{1}{16}$ -inch wall, connected by a metal adapter.

Standard glass Luer syringes: 5 c.c. capacity, 2 c.c. capacity.

Hypodermic needles: Gauge 27, length  $\frac{1}{2}$  inch; gauge 19, length 2 inches.

It is most important that needles be sharp and smooth edged. A rough or dull needle inflicts pain on the patient and catches in the tissues, irrespective of their density, thus hindering the operator in deciding what tissue he is penetrating.

**Solutions.**—Five per cent. phenol solution; amount sufficient to fill one bottle.

Sterile novocaine, 0.5 per cent. solution. This should be freshly autoclaved for hospital use. For office use, autoclaved, sealed, 10 c.c. ampoules, which are never more than 1 or 2 weeks old are recommended.

**Site of Puncture.**—The needle should be inserted far enough above the diaphragm so that the needle will not injure it, as the diaphragm has a tendency, particularly on the left side, to rise high when the patient lies on the right side in the prone position. The puncture should be made as far as possible away from any active lesions, thickened pleura, great vessels

(such as the subclavian), and important viscera. From the midaxillary line posteriorly, the point of puncture may be almost anywhere in the interspace except just under the rib around to that point. When entering anteriorly, it is well to go as close as possible to the upper edge of the rib, because the blood vessel and nerve are more likely to be located in the middle of the interspace.

*Antisepsis.*—After the operator has scrubbed his hands for at least 10 minutes, the sterile rubber gloves are put on.

Sterilization of the skin is best accomplished by applying a pledget of cotton saturated with untinted tincture **metaphen**, 1:200 solution, for 1 minute at the point to be punctured.

*Anesthesia.*—The skin and subcutaneous tissue at the point to be entered is infiltrated with 1 to 1.5 c.c. (16 to 24 minims) 0.5 per cent. **novocaine solution**, using the  $\frac{1}{2}$ -inch, 27-gauge needle and the 2 c.c. syringe.

The 5 c.c. syringe is attached to one end of the 3-way stopcock which is made to receive the tip of the syringe. Directly opposite this end, the tip of the stopcock is made to fit a hypodermic needle and to this end the 19-gauge needle is attached. The syringe is filled with the 0.5 per cent. novocaine solution. Then the  $\frac{1}{8}$ -inch end of the sterilized piece of rubber tubing is put onto the third end of the stopcock and the  $\frac{3}{16}$ -inch end of the tubing is attached to the proximal bottle.

The needle is held perpendicular to the skin at the point already anesthetized, low in the intercostal space. The skin is held taut with the left hand and with the right hand gentle pressure is exerted on the needle with a rotary motion. As the needle advances, novocaine solution is injected. In this manner, the deeper chest wall structures, including the parietal pleura, are anesthetized. The parietal pleura is detected by the feeling of dense, "springy" resistance. This is the time, when doing an initial collapse, for patient and slow advancement of the needle. Free pleural space is often indicated by the novocaine solution suddenly being sucked from the syringe into the pleural cavity. The valves are then turned, in order to hook up the needle with the water manometer. This opens the manometer to chest pressure. When the manometer shows negative fluctuations, which indicate and thus substantiate the fact that the needle is in the free pleural space, the needle is carefully immobilized.

*Instillation of Gas.*—The gas is instilled into the pleural cavity to effect pneumothorax.

Either **nitrogen** or **air** is used; both are equally satisfactory.

By syphoning the phenol solution from the distal bottle into the proximal bottle, pressure is brought upon gas in the proximal bottle. The gas is forced from the proximal bottle through the sterilized rubber tubing attached to the 3-way stopcock and then through the needle and into the pleural cavity. The amount of fluid syphoned from the distal bottle into the proximal bottle is equal to the amount of gas instilled into the pleural cavity.

The amount of gas given to the patient depends upon the chest pressure, as indicated on the manometer. In an initial treatment, usually not more than 300 c.c. of gas are instilled in the average-sized thorax. Gas is never given to the point of a positive pressure.

When refilling cases, the pressure should be kept slightly under "O" at the finish of the treatment. A complete collapse should be pushed by frequent refills (every day or two) until the desired collapse of the infected tissue is secured. The pressure may then be diminished until the uninfected tissue reëxpands, which it will do in advance of the infected tissue. This gives a maximum breathing capacity with maximum collapse of the diseased lung tissue, *i. e.*, *The Selective Collapse*.

In discussing his x-ray observations on the effect of artificial pneumothorax, N. F. Pershina (Problemy Tuberk. 1: 90, 1936) states he believes that the extent of reparative processes in a collapsed lung is determined by the type and the age of the lesion and by the duration and completeness of the induced pneumothorax. It appears from the x-ray studies of the Leningrad Tuberculosis Research Institute that early infiltrating lesions with a tendency to breaking down require not less than 4 years to heal and bring about permanent recovery. Patients presenting fibrous caseating lesions require from 5 to 6 years of pneumothorax therapy to obtain a permanent x-ray and clinical recovery. Interruption of the collapse therapy at an earlier period leads to recurrences with cavity formation after 3 or 4 years, especially if the patient lives under unhealthy conditions. Recur-



rences likewise occur in cases in which the pneumothorax is complicated by the formation of adhesions. It is advisable, therefore, to sever the adhesions even for cases in which the cavities heal and the tubercle bacilli disappear from the sputum. Diminution of the pulmonary area and its aeration observed roentgenologically after a prolonged collapse therapy suggest that considerable anatomic changes take place within the pulmonary parenchyma. The effectiveness of the artificial pneumothorax therapy can be judged from the fact that fibrous caseating lesions may heal under its influence and even become calcified. Such results are only rarely observed in conservative treatment.

Displacement of the heart and the mediastinum toward the collapsed lung need not necessarily be due to alterations in the pleura, as was formerly believed, but may be the result of cicatrizing alterations that existed in the lung previous to induction of pneumothorax or due to the effect of a prolonged compression of the pulmonary tissue.

*Bilateral Artificial Pneumothorax.*—H. F. Carmen (Am. Rev. Tuberc. 33: 491 (Apr.) 1936) states that before bilateral collapse is instituted it is important for the operator to be fully cognizant of and competent in the event that any of the many possible difficulties occur. A thorough understanding of the physiology of the cardiorespiratory system is important. The decreased blood flow through the collapsed lung tissue is compensated for by a speeding up of the blood flow through uncompressed lung tissue. When the intrapleural pressure is positive in a bilateral pneumothorax case, in the absence of adhesions, the lesser circulation becomes embarrassed and strain is thrown on the right ventricle of the heart and the patient suffers dyspnea. When moder-

ately high bilateral negative intrapleural pressures are maintained, the cardiorespiratory balance is sustained in the following manner: (1) by compensatory emphysema of normal lung tissue on both sides; (2) by speeding up the flow of blood through the uncompressed lung tissue; and (3) by increase in the sluice of blood through the capillaries.

The patient's vital capacity is of importance. When 500 c.c. of air are placed in each pleural space, the patient loses 1000 c.c. of breathing capacity and the cardiorespiratory system must compensate for this loss. Therefore, when the vital capacity is below 2000 c.c., bilateral collapse is inadvisable. It is not advisable to refill both sides on the same day.

The utmost care must be exercised in selecting cases for bilateral pneumothorax.

#### INDICATIONS:

1. Limited progressive bilateral disease without cavitation.
2. Bilateral cavitation, preferably the moth-eaten type.
3. Reactivation of trouble in the contralateral lung.
4. Uncontrollable hemoptysis in the opposite lung.
5. Occasionally pleurisy, with effusion in the opposite pleural space.
6. Acute tuberculous pneumonia, when the process is not too acute and extensive.

#### CONTRADICTIONS:

1. Extensive bilateral lesions with or without cavitation.
2. Large thickened wall cavities that resist compression.
3. Extensive fibroses in both lungs.
4. In successive bilateral pneumothorax when a large cavity in the initial lung resists compression.
5. Extensive pleuritic adhesions. A satisfactory collapse can rarely be obtained in the presence of this difficulty.

6. Low vital capacity, below 2000 c.c.  
 7. Patients above 40 or 45 years of age. After the fortieth year is passed, the cardiorespiratory system fails to compensate well.

8. Extensive extrapulmonary complications. Tuberculous laryngitis is not a contraindication. It is usually very materially helped by stopping the cough.

9. Threatening cardiac decompensation.

10. Extremely low vitality and marked toxemia.

J. N. Corsello and R. M. Bruckheimer (Am. Rev. Tuberc. 33:502 (Apr.) 1936) do not advocate that all cases of advanced tuberculosis be subjected to bilateral pneumothorax irrespective of the patient's condition, but that the measure should not be considered an agency of last resort.

Cases that are obviously terminal or those in which the patient is dyspneic even while at rest because of extensive disease should not be subjected to the treatment. Those presenting caseopneumonic lesions respond most poorly to the treatment.

*Complications* occurring during the course of treatment are the same as in unilateral pneumothorax; the most spectacular and distressing complication is that of a ruptured lung. While complications do occur more frequently than in unilateral pneumothorax, this increased incidence is not great enough to contraindicate its use.

Coulaud, among others, advises that patients with clinical tuberculous enteritis should not be treated by this method. However, while an involvement such as this undoubtedly adds to the hazards of the case, recovery is possible in certain instances if satisfactory pulmonary collapse is obtained. It was found that all the patients who had intestinal tuberculosis and in whom the result was unsuccessful, without

exception had unsatisfactory collapse of one or both sides. It is conceivable that with effective pneumothorax the result might have been different. One patient, who was gravely ill and had a severe intestinal involvement, made a gratifying recovery after both lungs were effectively collapsed.

Of 36 patients having advanced pulmonary tuberculosis treated by bilateral simultaneous artificial pneumothorax, 21 are still alive, in 18 of whom the disease is arrested or apparently arrested, and 2 are improved. One has suffered a recent reactivation of the disease after being well for 2 years, 1 year of which was after termination of treatment. Seven of those now living have returned to work. Nine others should be able to work in the near future.

**PHRENICECTOMIES VS. PHRENIC ALCOHOLIZATIONS.**—The promise originally offered by *phrenicectomy* has not been fulfilled, according to W. Jullien (Paris méd. 1:28 (Jan. 4) 1936). Its principal *disadvantages* are that it paralyzes the diaphragm without insuring favorable therapeutic results; it sacrifices healthy pulmonary tissues; and it may cause accidents.

Alcoholization of the nerve has some of the same disadvantages, but its effects are only temporary. It also has the advantage of avoiding the mechanical trauma produced by phrenicectomy and of allowing a tentative trial of the effect instead of a final irreversible one.

Alcoholization of the phrenic nerve, therefore, is usually preferable to phrenicectomy in cases in which pneumothorax is inadvisable. Ambulatory treatment is, of course, wholly inadvisable.

**PARALYSIS OF DIAPHRAGM.**—L. O'Shaughnessy and J. H. Crawford (Lancet, 1:534 (Mar. 7) 1936) do not consider phrenic evulsion, discreetly and carefully performed, a dangerous operation, but have adopted *phrenicosthasty*

or phrenic crush on quite other grounds. There is an increasing number of patients with bilateral phthisis for whom some form of bilateral collapse operation would offer a prospect and the only prospect of a cure, but a paralyzed diaphragm has ruled out such a possibility.

In the young patient a paralyzed hemidiaphragm does not produce signs of respiratory distress. But it has been suggested recently that in middle age paresis of the diaphragm may constitute a more serious handicap. Kochs found that phrenicotomy produced a greater reduction of vital capacity in middle aged than in young patients. The possible detrimental effects of the paralysis on cardiovascular function in later life must also be borne in mind, and the recent experiments of Nissen and Wustmann on the effect of diaphragmatic movement on the caval blood flow are of interest in this connection.

It is of advantage, therefore, for the patient to have a healed tuberculous lesion and a moving diaphragm, for, should the lesion again become active, the patient is a suitable subject for any form of treatment that may be necessary. If, on the other hand, the disease remains permanently arrested, there is no chance of the patient having to pay for this benefit by an impairment of respiratory or cardiovascular function in later life.

**PHRENIC PARALYSIS.**—P. Slavin (Am. Rev. Tuberc. 32: 535 (Nov.) 1935) discusses the 4 groups of cavernous cases in which phrenic procedures lead to exacerbation of destructive processes: excavated exudative and large fibrocaceous lesions, large subpleural cavities, and cavities in advanced fibroid tuberculosis.

In 7 cases, intended artificial pneumothorax was replaced by phrenic paralysis, because of failure to find a free pleural space. Though further enlargement of cavitation could be expected

in those cases under treatment by rest alone, the sequence of events showed that paralysis of the diaphragm was responsible for additional damaging processes. Two of the cases with excavated exudative and large fibrocaceous lesions developed postoperative stagnation of sputum in the cavities and accelerated detachment of caseous tissue, resulting in a rapid spread of the cavitation and massive extension of disease. An air-filled portion of a cavity may become obscured after operation by retained sputum or by approximated adjacent infiltrated areas, the x-ray picture simulating postoperative obliteration of the cavity. In large subpleural cavities, phrenic paralysis causes impairment of drainage, leading to progressive destruction within the walls of the cavity. In cases with excavated advanced fibroid tuberculosis there may be a dangerous postoperative reduction of their depleted vital capacity.

In all four groups, high elevation of a paralyzed diaphragm does not seem to diminish the untoward effect of the operation.

*Complications.* — *Gastrointestinal symptoms* following left-sided phrenic paralysis are not uncommon. Stanbury has reported 2 fatal cases. F. B. Trudeau noted a number of cases which, while the disturbances lasted for a week or even several months, always eventually cleared up.

H. C. Ballou, H. M. Wilson, J. J. Singer, and E. A. Graham observed cases of *eventration of the diaphragm* in which a permanently large stomach bubble under the highly arched diaphragm reached to the level of the third intercostal space. It was found that when left-sided phrenicectomy was followed by a marked rise of the left side of the diaphragm, there was an increased angulation of the abdominal portion of the esophagus. No experimental evi-

dence was found, however, to indicate that phrenicectomy results in obstruction of the lower part of the esophagus, or proof that phrenicectomy may produce cardiospasm.

C. A. Thomas and F. R. Harper (J. Thoracic. Surg. 5: 507 (June) 1936) report 4 cases of *acute dilatation of the stomach* following left sided thoracoplasty which was done after phrenic paralysis on the left side.

Case 1, a male, aged 41 years, had a history of advanced pulmonary tuberculosis of 7 years' duration, with bilateral cavitation, and a left-sided phrenic exeresis. Examination revealed the lesions in the right lung almost completely healed, but a large apical cavity in the left lung. His blood-pressure was  $120/80$ ; his pulse rate was 80. X-ray examination showed a 9.5 cm. rise of the left hemidiaphragm. An electrocardiogram showed slight myocardial damage with no other change. A first-stage thoracoplasty in which the upper 3 ribs were removed was done. The patient's condition was satisfactory until the fourth postoperative day, when the attending nurse insisted that he drink an eggnog. The patient had stated at the time he gave his history that he was sensitive to milk. Within 30 minutes after drinking the eggnog, the patient started to vomit and became dyspneic and cyanotic. His pulse was rapid and thready; the point of maximum intensity of the heartbeat was at the third intercostal space inside the midclavicular line. He was tympanitic from the fourth intercostal space to the base, and no breath sounds were heard on the left side. X-ray examination showed an enormous dilatation of the stomach extending to the third intercostal space. The patient died within a few hours.

At necropsy, the stomach was tremendously dilated, extending as high as the third rib at the anterior axillary line. The diaphragm was atrophic but not ruptured. The mediastinum was markedly displaced to the right. The left lung was well collapsed by the thoracoplasty and the elevated diaphragm, forming a small pyramidal mass which filled the space above the dome of the diaphragm. There was a compensatory emphysema of the right lung.

Case 2 was a male, aged 26 years, who gave a history of advanced pulmonary tuberculosis of 2 years' duration. He had had a temporary phrenic interruption on the left side 6 months previously. No abdominal distress had been

noted following the phrenic operation. His blood-pressure was  $130/110$  and his pulse rate 76. The x-rays showed a 4.5 cm. rise of the left hemidiaphragm. Two days after an upper stage thoracoplasty, in which 3 ribs were removed, the patient became greatly distended and complained of abdominal pain. He was dyspneic and cyanotic. His pulse was thready and the rate rose to 150 per minute. He was placed in an **oxygen tent**, which made him more comfortable, but the distention, dyspnea, and cyanosis continued until he died on the fourth postoperative day.

Autopsy showed the stomach dilated and reaching the third intercostal space. The intestines were very much dilated and the mediastinum was pushed to the right. The left lung was completely collapsed.

Case 3 was a male, aged 42 years, who gave a history of having had pulmonary tuberculosis for 8 years. Left phrenic exeresis had been done 4 years previously. Examination showed a huge cavity at the left apex. His blood-pressure was  $108/82$  and his pulse rate was 84. X-ray revealed a 5 cm. rise of the left side of the diaphragm. An upper stage thoracoplasty was done which included the first three ribs. The patient complained of abdominal distress and pain on the left side, but made an uneventful recovery from the operation. The second stage of the thoracoplasty consisted of removal of the fourth and fifth ribs. After this the patient had pain in the lower part of his chest but made a satisfactory recovery. The third stage operation was an anterolateral thoracoplasty, after which the patient had no distressing symptoms. The fourth stage operation consisted of removal of the sixth and seventh ribs. One hour after the operation the patient became dyspneic and complained of pain along the left costal margin. Fluoroscopy showed the diaphragm elevated to the second intercostal space, due to acute dilatation of the stomach. A **tube** was passed through the patient's nose into his stomach. This was drained continuously according to O. H. Wangenstein's method. Within a few minutes about 2000 c.c. of gas was withdrawn and there was immediate relief from pain and dyspnea. The tube was withdrawn on the third day. Again the patient became dyspneic and complained of rhythmic pains in the left upper quadrant of the abdomen. Reinsertion of the tube again brought relief. Two days later, it was removed. The symptoms recurred, so the tube was again inserted. After the seventh postoperative day, it was not

necessary to leave the tube in place continuously, but it was reinserted 3 different times for short intervals whenever there was a recurrence of the pain in the left upper quadrant of the abdomen. The patient's temperature and pulse dropped to normal and remained there for the duration of his convalescence, and he made a satisfactory recovery.

Case 4, a female, aged 40 years, gave a history of pulmonary tuberculosis of 14 years' duration. Examination revealed a large cavity in the left apex. Her blood-pressure was 110/80 and her pulse rate 96. She received artificial pneumothorax for 3 months, after which a left phrenic exeresis was done and then she received pneumothorax treatments for 6 months longer. The diaphragm did not rise following the phrenic paralysis in the presence of the pneumothorax, and there was no abdominal distress. Pneumothorax treatments were stopped and a first stage thoracoplasty was done. The first, second, and part of the third ribs, were removed. The patient made a satisfactory, uneventful recovery. A second posterior stage operation, which included the removal of part of the third, and the fourth and fifth ribs, was done and from this operation the patient also made a satisfactory recovery. Later, an anterolateral stage was performed with no ill effects. Then, a third posterior stage operation was done. At this time the sixth, seventh, and eighth ribs were removed. Within an hour after the operation, the patient became cyanotic and dyspneic, and her pulse rose to 140 and was thready. Her condition was recognized as acute gastric distention and **continuous suction** was started with almost immediate improvement. Continuous suction was maintained for 48 hours, after which the patient was improved and continued to convalesce to a satisfactory recovery.

**COMPLEMENTARY ANTERIOR THORACOPLASTY.**—In certain cases of pulmonary tuberculosis, C. Haight (J. Thoracic. Surg. 5:453 (June) 1936) believes that **complementary anterior thoracoplasty** is an important adjunct to **posterolateral thoracoplasty**. It provides the additional collapse necessary to effect and maintain the closure of cavities that cannot be closed by posterolateral thoracoplasty alone.

An important reduction of the operative mortality and morbidity has resulted

from performance of the thoracoplasty in a horizontal plane as well as in the usual vertical plane.

Parasternal division of the costal cartilages with resection of the remaining anterior costal stumps is done. The cartilages, with the exception of the first, which is resected, are hinged at the sternum so that they may swing posteriorly and mesially, thereby increasing the pulmonary collapse. As the cartilages are not resected, stability of the thoracic wall is obtained eventually, whereas the former technic with resection of the cartilages resulted in a permanently soft anterior thoracic wall due to failure of the residual perichondrium to develop firm cartilage. Preservation of the cartilages also decreases the anterior deformity.

**RESPIRATION, MECHANICS OF.**—The mechanisms of respiration have been investigated from an entirely new and novel approach by P. M. Andrus (Am. Rev. Tuberc. 33:139 (Feb.) 1936). He showed the mechanisms and statics of the pleura, the mechanisms of inspiration, pulmonary statics and dynamics, the expansion of the bronchi, and, finally, the mechanisms of expiration.

**Mechanics of Pleura.**—The pleural surfaces are normally moist with a thin but definite layer of liquid. This means that the normal pleural cavity is not "empty," but contains a layer of liquid between the pleural surfaces. Therefore, the pleural sac must be treated from the physical standpoint as an actual body-cavity with contents, and not as a "potential" or "nonexistent" space.

**Statics of Pleura.**—From within the lung the visceral pleura is exposed to the atmospheric pressure of the contained gas. Opposing this force, however, is the elastic traction of the stretched lung, which is customarily

stated to be 10 mm. Hg. at the end of inspiration. The algebraic sum of these forces is 750 mm. Hg., and this is the force to which the intrapulmonary surface of the visceral pleura is subjected. This is the pressure which the contents of the closed pleural sac assumes. The pressure is less than that of the intrapulmonary gas, and this difference constitutes the "negativity" of the pressure in the pleural space. The latter is thus due to, and is also exactly counterbalanced by, the elastic traction of the stretched lung. It is greatest at the position of full inspiration because the lung is stretched to the greatest degree and exerts the greatest elastic pull at this phase of the respiratory cycle. If the lung exerted no elastic pull, the pressure in the contents of the pleural space would be the same as that of the gas within the lung.

At positions of respiratory rest, therefore, the visceral pleura lies at a position of complete equilibrium as to the stresses to which its opposite faces are subjected. Although the pressure of the gas in the lung is greater than the pressure of the contents of the pleural space, the former represents only a part of the forces in effect, the pressure difference being exactly neutralized by the elastic traction of the stretched lung.

**Mechanics of Inspiration.**—An analysis of the physical conditions involved indicates that it is impossible to explain the expansion of the lung as an inflation, due to gas pressure. The pulmonary air-chambers are normally expanded by a process of direct traction by the outward-moving thoracic walls, and the flow of gas and the gas-pressure changes are secondary to, and in no way a cause of, the expansion of the lung. From these considerations, certain deductions are warranted as to the nature and distribution of mechanical stresses in the lung, which have a direct bearing

upon the concepts of the pathogenesis of pulmonary diseases.

**Pulmonary Statics.**—The elastic tension of the lungs and their constituent collapsible chambers are maintained by reason of anchorage at the surface to the surrounding thoracic walls. This attachment is due to the cohesive and adhesive properties of the normal layer of pleural liquid and the pleural membranes, the value of these being considerably in excess of any counterforce that may arise in the living subject.

The patency and elastic tension of the multiple collapsible air-chambers of the lung is maintained by reason of mechanical anchorage to the more rigid and muscular peripulmonary walls, and this physical state cannot be explained as a gas-pressure effect.

**Pulmonary Dynamics.**—As inspiration proceeds the visceral pleura, because of its physical attachment to the thoracic walls, must immediately and intimately follow every movement of the latter. The initial outward movement of the visceral pleura is a mechanical outward displacement of one wall of each of the immediately subpleural air-chambers. Such movement constitutes expansion of these chambers. This is the initial event in expansion of the lung and until this occurs, no expansion of the remainder of the lung is possible. This initial inspiratory movement produces expansion of the remainder of the lung by traction through its solid tissues.

The human lung is composed of highly elastic material and under normal conditions is stretched in a state of elastic tension even at the position of the greatest possible expiration. The initial outward movement of the visceral pleura is therefore necessarily accompanied by a simultaneous lengthening of the elastic of the lung in all directions in which the pleura moves. The stress is distributed equally throughout any axis of motion.

Each elastic axis in the lung is a series of connected air-cell walls, and lengthening of any axis means a simultaneous expansion in that direction of each related air-chamber. The total outward movement of the pleura in all directions predicates a simultaneous expansion of all the elastic air-chambers throughout the lung.

The essential factor that indicates that the multiple air-chambers throughout the lung are normally expanded by traction from the periphery and not by gas-pressure is the time element involved in the production of effects by these two methods. An inflation necessitating a flow of gas from one place to another, requires a measurable period of time. In the case of the multitudinous minute air-channels of the lung, the lag in the flow of gas is relatively pronounced. Transmission of the expansile force along the elastic tissue of the lung can be associated with no measurable time lag in relation to the causative motion, in accordance with the physical laws of transmission of energy in an elastic. For this reason, the air-chambers of the lung are normally expanded by traction on their elastic walls from the periphery before it is possible for this result to be attained by gas-pressure.

**Pulmonary Gas-pressure and Stresses.**—Since the expansible air-chambers are expanded simultaneously and not serially throughout the lung, the gas-pressure falls, not progressively from periphery to hilum, but simultaneously throughout these expansible units. The air flows into the air-sacs from the relatively non-expansible bronchial reservoir because of the pressure difference thus set up between the dilatable and nondilatable chambers of the lung.

The exact uniformity of gas-pressure distribution and mechanical stress in different parts of the lung is dependent upon the variation in elasticity of dif-

ferent parts of the lung; upon the ratio of the size of the gas-chambers to the amplitude of excursion of the thoracic wall in any direction; and upon the freedom of the lung to adapt itself to the varying shape of the chamber in which it is contained. Thus, C. C. Macklin (Am. Rev. Tuberc. 25:393 (Mar.) 1932) has pointed out that pathological fixation of the hilum may be expected to prevent proportionate expansion of those parts of the lung situated posteriorly and above this region. The interalveolar pores, as described by C. C. Macklin (J. Anat. 69:188 (Jan.) 1935) and C. M. Van Allen, G. E. Lindskog and H. G. Richter (J. Clin. Investigation 10:559 (Aug.) 1931), play a decisive part in equalizing pressure differences resulting from minor unevenness of expansion, and thus protect the air-cell walls from resulting mechanical stress.

**Expansion of Bronchi.**—C. C. Macklin (Am. Rev. Tuberc. 25:393 (Mar.) 1932; Tubercle 14:16 (Oct.) and 14:69 (Nov.) 1932); Physiol. Rev. 9:1 (Jan.) 1929) has shown that elongation of the bronchi is an essential element in the expansion of the lung and that without such elongation the respiratory tissues would be splinted and immobilized. It has also been shown by bronchoscopy, and by radiography after the instillation of radiopaque material, that the bronchi increase in diameter with full inspiration, although the effect is not visible during quiet respiration.

Since the inspiratory expansion of the bronchi is not primarily a gas-pressure effect, it must be concluded that they are dilated by the mechanism which causes the expansion of the remainder of the lung, *i. e.*, mechanical traction from the receding thoracic wall operating through the intervening respiratory tissues. Although the individual air-cell walls are very delicate, the sum of

the large numbers of walls provides a tractile medium of ample strength.

The same mechanism must provide the motive force by which the bronchi are elongated during inspiration.

**Mechanics of Expiration.**—During inspiration a reserve of energy is provided and stored up by the muscular efforts, which may be released to produce a passive or non-muscular expiratory movement. This reservoir of energy is of two types: (1) the effect of gravity on the thoracic walls by which the downward and inward lever movement of the ribs reduces the volume of the thoracic cavity; and, (2) the increased elastic tension of the lung resulting from the expansile movement.

During normal breathing, as the thoracic walls move inward and the dimensions of the lung are shortened, the resulting slack in the lung tissue is taken up simultaneously by the contraction of the pulmonary elastic. Were this not the case, the pleural pressure would become positive during expiration. During the progress of normal expiration, the following physical conditions may therefore be inferred:

(1) The state of tension in the lung is at least approximately uniform throughout the course of any elastic axis.

(2) The degree of expansion of the multiple air-chambers, the walls of which comprise any elastic axis, is approximately uniform.

(3) The gas-pressure is approximately uniform throughout any such periphery-to-hilum series of air-cells.

**STERILIZATION OF OPERATING ROOM AIR.**—SPECIAL BACTERICIDAL RADIANT ENERGY, Results of the Use in Extrapleural Thoracoplasties.—D. Hart (J. Thoracic. Surg. 6: 45 (Oct.) 1936) believes that pathogenic bacteria given off by human beings and floating in the air cause the major

portion of infected wounds originating in the operating room, and that special bactericidal radiation will eliminate this hazard of infection and is the only practical means available at this present time.

When a Petri dish of sterile blood agar was exposed for one hour to the air in any operating room, while it was being used, and then incubated for 24 to 48 hours, it showed many colonies of *Staphylococcus aureus*, at times as high as 78. The total number of colonies of all organisms (predominantly *Staphylococcus aureus*, hemolytic and non-hemolytic, and *Staphylococcus albus*) was occasionally as high as 150.

As surgery has embraced operative procedures of greater magnitude and with inevitable trauma, and as sterilization of everything but the air has become more satisfactory, this danger of air-borne bacteria, once of little significance, has now assumed a major rôle. The increasing use of the operating room space has added to this hazard by increasing the pollution of the air. With large numbers of visitors, the air contamination is increased. Most of the staphylococci which cause infections reach the wound by way of the air rather than by skin contamination. Without sterilization of the air, as by the use of the bactericidal radiation, every operative wound is contaminated. At times these organisms are quickly killed or walled off by the host, while at other times they may go on to suppuration or even cause the death of the host.

The postoperative temperature rise of the first few days is in most cases caused more by this bacterial contamination than by the absorption of blood and traumatized tissues. This does not take into consideration the reaction from compressing a tuberculous cavity which is infected. However, even in these cases, at times, the temperature ascribed



to this phenomenon may be caused more by bacterial contamination of the operative wound than by absorption of tuberculin products from the lesion in the lung.

Despite the general aseptic surgical technic, the number of infected wounds is still high (10 to 20 per cent.), as indicated by reports from clinics in which a careful survey has been made. The majority of these infections are so mild that the public and the profession have not become aroused. However, these infections may be greatly reduced by a barrage of radiation about the operative wound and supply and instrument tables, of such an intensity that any organisms floating in the air would be killed before they could land in a protected position.

A therapeutic **ultraviolet lamp** was found to be effective in killing a sprayed culture of hemolytic staphylococcus aureus at a distance of 8 feet from the lamp within 60 seconds. The carbon arc lamp was found to have practically no effect on the organisms.

In designing a source of radiant energy effective in destroying bacteria, care was exercised to see that the intensity and the distribution of the wavelengths capable of producing detrimental effects on tissue were so low that such effects were practically *nil*. It is important for lengthy operations, where long exposures are necessary, that any harmful burning action be avoided. However, it is also important that the radiation provided be sufficiently bactericidal to accomplish destruction of the bacteria without the intensity being of such a character as to create any discomfort to the patient.

To meet these requirements, a special radiant energy device has been constructed that is tubular in shape, has unheated electrodes, and utilizes a special gas mixture in which the discharge takes place with the production of the radiant

energy. During operation, the tube remains at a temperature only a few degrees above room temperature.

Two blonde volunteers were exposed to the radiation for 80 minutes and received only a slight reddening of the skin.

Following the use of the radiation during operations, patients had less post-operative pain, the temperature was lower, and healing was more rapid. All wounds made in the field of this bactericidal radiation maintained throughout the period of healing a dry, scaly appearance. This was in contrast to the occasional moist slightly macerated appearance of the suture line in certain thoracoplasties done without the use of bactericidal radiation.

For the operating staff who frequently are exposed to the radiation for long periods of time, no really satisfactory protection has yet been devised. Stiffly starched hoods and goggles made of plain glass which is impermeable have been used. They limit side vision, are hot, and become foggy. However, they can be made fairly comfortable by placing a suction tube beneath, to insure adequate ventilation. Occasionally sun-helmets and eye-shades have been used.

## THORACIC SURGERY.—

**Anesthesia in.**—U. H. Eversole and R. H. Overholt (J. Thoracic Surg. 5:510 (June) 1936) consider that anesthesia for major thoracic surgery presents many difficult problems.

Anoxemia, cyanosis, carbon dioxide accumulation, respiratory center stimulation, irregular and struggling respiratory movements, and a rising pulse have been frequent occurrences with ordinary types of anesthesia.

The absorbing surface of the lung is reduced, both in regard to the anesthetic agent and oxygen. The usual poor general condition of the patient, the re-

sult of continuous absorption of poisonous toxins, makes him intolerant of anoxemia.

Subarachnoid block or spinal anesthesia is not recommended, because of its depressing effect on the patient's condition.

**Avertin** (tribromethanol) is commonly used for general anesthesia without inhalation. The patient is easily anesthetized, and breathes quietly on the table, and there is no postoperative nausea. Avertin has been used in thoracic surgery as a basal anesthetic supplemented by gas, but is not entirely satisfactory. It causes a marked lowering of the blood-pressure and depression of the cough reflex and respiration that extends for several hours into the early postoperative period. In more than half the cases it causes a variable degree of cyanosis postoperatively, necessitating putting these patients into an oxygen tent for a day or more to relieve anoxemia and insure a safe convalescence.

Of the inhalation anesthetic agents, **nitrous oxide** is perhaps the most widely used in thoracic surgery. It is a nonexplosive, nonirritating, and controllable gas. To anesthetize a patient sufficiently, however, it must be administered in very high concentrations (90 per cent. or more) and the 10 per cent. or less of oxygen that the patient gets is not sufficient.

**Ethylene** permits a lower concentration of the gas (80 to 85 per cent.), but still this margin is too narrow to insure adequate oxygenation in the crippled pulmonary patient. Also, ethylene is explosive in lower concentrations.

**Ether**, administered by either an open or closed method, will provide adequate oxygenation for most patients. It is widely used to supplement nitrous oxide or ethylene. However, ether is irritating to the respiratory passages and it is the contention of many that quiescent tuberculous lesions are activated by its use.

**Acetylene** has been used considerably in Europe, but has had limited application in the United States. It permits higher concentrations of oxygen. A cumbersome apparatus is required for its use, however, and it is highly explosive.

**Cyclopropane** (trimethylene) which has been known only since 1928, has been found the most satisfactory as a general anesthesia for this group of patients. It may be administered in concentrations of 20 per cent. or less, with 80 per cent. or more of oxygen, thus suboxygenation is avoided. Cyclopropane gives a depth of anesthesia similar to that of ether and needs very little absorptive surface in order to reach a sufficiently high concentration in the blood to maintain surgical anesthesia. The blood is hyperoxygenated by quiet shallow excursion of the thoracic walls. During administration of the anesthesia, the venous and arterial bloods grossly give the same oxygenated appearance, even in patients with vital capacities limited to one-fourth their estimated normal (900 to 1400 c.c.).

Cyclopropane is as inflammable and explosive as ethylene when mixed with almost all proportions of oxygen. With precautions, there is little practical danger. Static spark must be avoided and it must be administered in an entirely closed system.

**Cyclopropane combined with the carbon dioxide absorption method** approaches most closely the ideal for general anesthesia in surgery of the thorax. The anesthetic mixture is re-breathed throughout the entire operation. **Oxygen** is added at a rate sufficient to satisfy the metabolic needs of the body. The carbon dioxide is extracted by passing the gases through soda lime. The carbon dioxide accumulation causes a quiet type of respiration without forceful movements of the thoracic cage. This system is economical and the explosive

hazard is greatly minimized by preventing the liberation of gases in the operating room.

The intrapulmonic pressure should be under the control of the anesthetist at all times. Uneven, jerky, violent, or wide excursions of the chest may spread an acute inflammatory process or tear a fibrotic lung. The anesthetist should be able to increase or decrease the depth of anesthesia at will.

In a closed system the intrapulmonic pressure is under direct control of the anesthetist. The danger of over-distention of the lungs by pressure upon the bag can be eliminated by having in the gas circuit an escape valve adjustable to different degrees of pressure.

Accidental opening of both pleural cavities makes spontaneous respiration impossible and necessitates immediate artificial respiration. This may best be accomplished by rhythmic manual pressure on the rubber breathing bag containing the anesthetic mixture. If an inhalation anesthetic is being administered by means of an entirely closed system, this is very easily done and can be kept up indefinitely. Seven to eight millimeters of mercury pressure is sufficient to prevent collapse of the lung, and a pressure of 20 to 22 mm. should not be exceeded. The need for positive pressure when the pleural cavity on only one side has been opened has been greatly exaggerated. It is rarely necessary to add to the pressure in the closed system. Positive pressure is needed, however, when the pleural cavity is opened in the presence of a contralateral pneumothorax. Sudden and accidental pneumothorax on one side may cause a patient to go into collapse from a quick shifting and subsequent flapping of the mediastinum. This will not occur if the closed system is being used at the time the opening is made, and if immediate positive pressure is established.

The patient's position on the table increases the chance for a spill-over of secretions into the good lung, and the compression of the lung during and after thoracoplasty may be sufficient to force enough fluid or purulent material into the bronchi and trachea to cause asphyxia if such material is aspirated into the dependent lung. Hemorrhage into the bronchus during the course of an operation may be of such magnitude that the patient virtually drowns in his own blood.

**Aspiration** of the tracheobronchial tree should be possible during the course of an operation. A suction pump with a number 16 F catheter is convenient for nasal passage and also for pharyngeal aspiration. If an intratracheal tube is in place, this catheter can easily be passed down within the lumen of the intratracheal tube, and any fluid which accumulates in the trachea or primary bronchi can be aspirated. If an intratracheal tube is not in place, it should be inserted immediately when the first evidence of an accumulation in the air passages occurs.

While the patient is on the table, his position limits mechanically the function of the good lung, and *respiration* may become *obstructed*. This may usually be relieved by the use of nasal or oral **breathing tubes**. If the obstruction is low down, an **intratracheal catheter** should be inserted. As the patient's table position makes it difficult to insert an intratracheal catheter, this should always be done before the operation starts if for any reason the anesthetist suspects that a serious obstruction may develop. In cases in which one or more lobes of the lungs are to be removed, an intratracheal catheter should be routinely used. Also, an intratracheal catheter should be inserted in all cases of bronchiectasis and lung abscess. It can be used to advantage in some tuber-

culous subjects for thoracoplasty when excessive secretions are present and a general anesthesia is necessary. In the average thoracic case, more particularly thoracoplasty, serious obstruction is not sufficiently common to warrant the routine use of an intratracheal breathing tube. A **flexible metal catheter** is very satisfactory in thoracic cases. Because of its extreme flexibility and resistance to lateral compression, there is no danger of its kinking during the process of placing the patient into position for operation after the catheter has been inserted.

Concerning *preoperative medication*, the medication as well as the anesthetic agent must not extend their influence on respiration and the cough reflex into the few hours immediately following the operation, particularly in cases of lung abscess or tuberculosis, where the diseased lung has not actually been removed and internal drainage of these areas aided by the cough reflex must not be interfered with.

When cyclopropane is used, consciousness is regained within 3 to 10 minutes. The cough reflex returns with equal rapidity. Nausea and vomiting occur in about one-fourth of the patients in the first 3 minutes, but in only one-tenth subsequently.

**Cyclopropane**, in contradistinction to ethylene and nitrous oxide, is not a respiratory stimulant. Hence, preoperative medication of a respiratory depressant nature, such as the opium derivatives, should be used in much smaller dosage than in preparation for anesthesia other than cyclopropane. In addition, cyclopropane is a sufficiently strong anesthetic agent to maintain surgical anesthesia of sufficient depth without the aid of heavy preoperative medication. Since scopolamine is not a respiratory depressant, it is not necessary to decrease the dosage of this drug propor-

tional to the decrease in opiate dosage. An average dose ranges from  $\frac{1}{32}$  to  $\frac{1}{64}$  grain (2 to 1 mg.) of **dilaudid** (dihydromorphinone hydrochloride) and  $\frac{1}{150}$  grain (0.45 mg.) of **scopolamine hydrobromide** given subcutaneously 1 hour before operation.

IN LOBECTOMY.—I. W. Magill (Proc. Roy. Soc. Med. 29:643 (Apr.) 1936) states that the presence of disease in the organs involved in respiration places many thoracic operations in a special category from the standpoint of anesthesia. The poor general condition of the patient, his position on the operating table, and the necessity for aspiration throughout the course of the operation are all important factors.

One hundred twenty-eight patients were anesthetized and subjected to lobectomy by the same surgical team. From this experience, it was found that preliminary medication should be short and active and recovery from the anesthesia should be rapid.

For general anesthesia, the administration of **omnupon** and **scopolamine**  $\frac{3}{4}$  hour before the operation and the intravenous injection of a minimal dose of **evipan** immediately before induction of the anesthesia is advised.

**Spinal anesthesia** was used for *lobectomy* and *pneumonectomy* in 23 cases. The patients were able to breathe quite well during the presence of an open pneumothorax and oxygen was rarely given.

In *high abdominal operations* the fall in the blood-pressure was quite marked when spinal anesthesia was used.

There is great danger in alternate bouts of cyanosis and oxygen inflation during general anesthesia in cases of pulmonary disease. **Cyclopropane** is of great value in surgery of the chest. It is favored over nitrous oxide and oxygen unless diathermy is to be employed. In the use of nitrous oxide and

oxygen alone there is some degree of suboxygenation. When *diathermy* is employed, **chloroform** is the only supplement which can be used without the risk of an explosion.

There are 3 alternative methods of **intubation**. One is the use of an endotracheal tube with a balloon cuff through which suction can be applied. This method is applicable at any age. Another method is the introduction into the main stem bronchus on the sound side of a tube with a balloon cuff to prevent the spilling over of secretions from the contralateral lobe. When such a tube is employed on the right side, there is danger of occluding the bronchus of the right upper lobe. This method is particularly suitable for pneumonectomy. The third method consists in the use of an intratracheal tube combined with the insertion into the bronchus on the affected side of a suction catheter bearing a balloon to close off the main bronchus. This method is favored for lobectomy.

For intrathoracic operations, a positive pressure is not important. There is danger in inflating a diseased lung, especially when sputum is abundant. The lowest pressure consistent with a smooth anesthesia should be employed.

**PHRENICECTOMY.**—*Postoperative Atrophy of Diaphragm.*—J. C. Galan, G. Fonseca and J. Dutrey (Prensa méd. argent. 23:427 (Feb. 12) 1936) state that the results of experiments and necropsies prove that a well performed phrenicectomy with ample resection of the phrenic nerve results in the production of atrophy of the muscles of the corresponding hemidiaphragm. The anatomopathologic study performed in 2 cases in which the paralysis of the diaphragm had lasted for 3½ years and for 8 months, respectively, showed that the hemidiaphragm corresponding to the phrenicectomized side

had undergone the following changes: intense atrophy of the muscle, a large part of which had disappeared and had been replaced by cellulofatty tissues, and intense alterations of the remaining muscular fibers, a large portion of which were dissociated and thinned. The anatomopathologic changes of the hemidiaphragm after phrenicectomy prove that the phrenic nerve is the one which controls movement of the diaphragm. If there is any collateral motor innervation due to the presence of intercostal, either contralateral or accessory phrenic nerves, or other nervous impulses, it is insufficient to maintain trophic conditions of the diaphragm after phrenicectomy and still more insufficient to maintain the motor functions of the diaphragm after the same operation.

**PNEUMONECTOMY.**—*Indications.*—Monod, of Paris and Bonniot, of Grenoble (J. A. M. A. 107:1649 (Nov. 14) 1936), state that the term “pneumonectomy” should be applied only to operations in which either the entire lung (total pneumonectomy) or one of several lobes (lobectomy) were removed, with ligation of the pedicle. To partial removal, the term “fragmentary pneumoresection” should be applied.

Two problems, the technical and the clinical, present themselves.

The *technical problem* includes the present knowledge of the anatomy, physiology, and pathology of the lungs. The last named is the most important from the surgical standpoint because of the great risks due to infection which it is necessary to prevent.

Methods of performing pneumonectomy and their *indications* can be divided into:

1. Cases in which there are no pleural adhesions.
  2. Cases presenting pleural adhesions.
- In lobectomy, the one-step method should be reserved for aseptic or slightly

infected cases. Two-step operations have a much lower mortality.

The surgeon must have trained assistants and special apparatus. It is preferable to operate in a relatively large room, in air that is conditioned and sterilized.

The *clinical problem* involves a study of the 3 *indications* for pneumonectomy that exist at present:

1. Primary cancer of the lung.
2. Bronchiectasis.
3. Pulmonary abscess.

*Primary cancer* constitutes from 7 to 8 per cent. of all cancers. The outcome, heretofore, has always been fatal, and at present no method of treatment other than pneumonectomy is available. Pneumonectomy can only be successful if the neoplasm involves only the first 2 cm. of the main bronchus and if no metastases exist in the pleura, chest wall, diaphragm, or mediastinal lymph nodes. Cases without recurrence in which operation was performed 5, 6, 7 and 9 years ago show that the cited essentials of success can be fulfilled. The types most suitable for operation fortunately include cases in which an early diagnosis is possible. Only total pneumonectomy, with separate ligation of the various components of the pedicle, should be attempted.

In *bronchiectasis* the question is, in which cases is pneumonectomy or lobectomy justified? It is the general opinion that bronchiectasis is a relatively benign condition, while pneumonectomy or lobectomy is a serious procedure. The prognosis of bronchiectasis is still an unsolved problem. If it could be shown that the majority followed a benign course, only the severe complicated cases could be considered as calling for operative measures. This, however, would confine surgery to hopeless cases, thus limiting the field in the future to cases with a potential high operative mortal-

ity. If, however, the clinician could learn to distinguish mild from severe cases at an early period, pneumonectomy would be able to forestall much future trouble.

In *abscess of the lung*, the only indication for pneumonectomy or lobectomy is in cases that do not improve under other forms of treatment. This would include single, old, centrally-located abscesses and those which are complicated by bronchiectasis.

Sargent (*Ibid.* 107:1650 (Nov. 14) 1936) claims that a progressive fragmentary pneumonectomy or even a simple pneumotomy will suffice for the majority of lung abscesses if carried out early. However, if operation is delayed until a progressive pyosclerosis complicated by secondary bronchiectasis develops and the lobe or lung is transformed into a veritable purulent sponge, more radical measures are needed.

In *chronic, fetid bronchiectasis*, regardless of the origin, nothing except operative removal can have any influence on a sclerotic mass of tissue penetrated by large dilated bronchi. Before a lobectomy is performed, however, a thorough exploration with iodized oil must be carried out to ascertain the condition of the other lobe or of the other lung, in the case of a pneumonectomy.

In *cancer of the lung*, the chief consideration is early diagnosis, because in addition to the serious operative risks, the postoperative complications in the form of overlooked metastases cannot be underestimated.

Bezançon (*Ibid.*) feels that much still remains to be learned concerning *bronchopulmonary suppuration*, and that it is only through frequent x-ray examinations, with and without iodized oil, as well as a study of the pathology and bacteriology, that a more accurate idea of the clinical picture can be gained. Every case must be considered individu-

ally, so that the chances for spontaneous recovery can be weighed as opposed to operation.

The principal indication for lobectomy, in the opinion of L. Kindberg (*Ibid.*), is in cases of *bronchiectasis*, if possible at an early stage. The classic theory "progressive sclerosis of the entire respiratory tract following recurrent, little understood infections" can be applied to only the minority of cases. There are 2 groups suitable for operation: (1) acquired dilatation of chronic nature or following a bronchiectatic abscess, and (2) superinfected congenital dilatation, a localized lesion. The prognosis in such cases is not favorable (from 8 to 10 years of life) and life soon becomes intolerable. It is logical, therefore, to undertake a radical treatment in such cases. Bronchiectasis with a benign clinical course, in aged patients, or generalized lesions, are to be excluded as potential operative cases. Lobectomy is recommended for these two groups of cases.

Edwards of London (*Ibid.*) prefers a one-step operation, independent of the condition of the pleura. One hundred and thirteen lobectomies (1 bilateral) were performed for bronchiectasis, with 16 deaths, a mortality of 14 per cent. Of 97 patients who survived the operation, 12 died (of intercurrent disorder or tuberculosis) from 1 to 5 years after the operation. Sixty-four patients are alive from 1 to 7 years after operation and 35 of these are free from any evidence of bronchiectasis. Seven total pneumonectomies have been done for bronchiectasis with 2 deaths (28 per cent.).

For *cancer*, 16 lobectomies were done, with 3 operative deaths (19 per cent.), 8 recurrences, and 6 cures (37 per cent.), dating back 2, 6, 7, and 9 years since the operation,

Six total pneumonectomies were done on patients from 31 to 63 years of age, with 2 operative deaths, 1 metastasis and 3 survivals.

*Technic.*—Certain improvements in the technic of pneumonectomy as well as in preoperative preparation and postoperative care have been made in the past two years. W. F. Rienhoff, Jr. (*Arch. Surg.* 32:218 (Feb.) 1936) bases following conclusions on the results obtained in 10 cases in which total pneumonectomy was performed and 20 cases in which thoracic exploration provided an opportunity for the observation of technical methods.

In the *preparation of the patient* for the operation it is of the greatest importance first, to induce, if possible, a complete collapse of the lung by a gradually induced pneumothorax, and second, to produce an inflammation of the parietal and visceral pleura in order to incite a serofibrinous pleurisy which will be followed by the formation of granulation tissue.

Adequate exposure of the hilus of the lung can be obtained through an anterior incision between the third and fourth ribs. Division or resection of a rib is unnecessary.

In the dissection of the hilum on the left side, the mediastinal pleura is opened and the mediastinal (extrapericardial) portion of the pulmonary artery is exposed. The dissection is facilitated by clamping the obliterated ductus arteriosus and rotating the artery. The intrapleural portion of the artery is only 0.5 cm. in length, as compared with the 2.5 cm. exposed by this method.

All vessels are ligated separately. In the treatment of the bronchus, the cartilaginous ring is clipped circumferentially and ligated with an encircling ligature or with interrupted ligatures of silk. It is of advantage to ligate the bronchus within the mediastinum, as

the surrounding areola is of value in the promotion of healing.

On the right side the superior pulmonary vein is ligated intrapleurally. The pulmonary artery should be dissected within the mediastinum after retraction of the superior vena cava, pulmonary vein, and left auricle. A posterior dissection is the safest approach. Careful and meticulous dissection of the lymphatics of the hilus should be done.

Closure is effected without drainage. Serum and plasma accumulations are not tapped. The space becomes obliterated by a fibrinous clot formation. Subsequent thoracoplasty is unnecessary.

Basal **anesthesia** induced with **tri-brom-ethanol** supplemented with **nitrous oxide** and **oxygen** is used. Intubation of the trachea is not necessary and is probably harmful because of the traumatization of the mucosa.

An **oxygen tent** is used routinely for from 24 to 48 hours after the operation. The patient is kept on the side operated upon in the Trendelenburg position for 48 hours. After this time the semi-sitting posture, with a change of position every 2 hours, is advisable.

**Readjustments Following Pneumonectomy.**—W. F. Rienhoff, Jr. (South. M. J. 29:445 (May) 1936), made an analysis of 36 pneumonectomized patients. Ten had had an entire lung removed, 24 cases had only a part of the lung removed, and in 2 of the patients posttraumatic atrophy of the left lung had occurred.

Compensatory changes occur in the thoracic cage and its contents after total and partial pneumonectomy, and there is a total absence of immediate or remote respiratory or circulatory embarrassment following these procedures. Thoracoplasty or the resection of ribs may be given up, certainly as a primary procedure, and in all probability, particularly in clean cases, it is unnecessary

to do any type of thoracoplastic operation. It is also unnecessary to do phrenicectomy before or during the operation of total or partial pneumonectomy.

It is the piston action of the diaphragm on that side against the rigid intact wall of the thorax on both sides that brings about the so necessary expansion of the remaining lobes following partial pneumonectomy, and it is, as a rule, either completely or practically immobilized on the operated side for some time following total pneumonectomy. It seems that at a later date the activity of the diaphragm on the operated side returns with the filling of the thorax by the dilatation of the contralateral lung.

Thus, it follows that interference with the normal anatomic or physiologic condition of the thoracic parietes after total or partial pneumonectomy may be unnecessary, if not actually harmful.

It is not advisable to drain the remaining empty space following total pneumonectomy, because this is immediately filled with a coagulated mass of plasma, which undergoes later organization, with the production of a fibrous tissue mass that occupies a space of greater or less size, depending on the cavity that eventually has to be filled. Not only in total, but also in partial pneumonectomy, if the remaining lung undergoes a compensatory dilatation, this multiloculated cystic mass of fibrous tissue is compressed by the encroaching lung or lobe and gives way as the space is occupied by the gradual enlargement of the remaining lung tissue, the final result being that the space which normally would be occupied by lung but is not, becomes filled by this labyrinthine cystic, fibrous tissue body. This may be so great—as in cases of total right pneumonectomy—as to occupy the entire remaining thoracic cavity or it may fill only a small portion.



**VAGUS IN RELATION TO LUNG SURGERY.**—Sudden death following operations on the lung has been thought to be due either to air embolism or stimulation of the vagi. In L. O'Shaughnessy's (J. Thoracic Surg. 5:386 (Apr.) 1936) experiments on dogs it was found that traction on the root of the lung produced an alteration in the respiratory and cardiovascular activities. When electrical stimulation of the anterior and posterior surfaces of the lung root was substituted for mechanical stimulation, stimulation of the posterior lung root caused an alteration in breathing. At times, an orthopnea was produced, while at other times there was observed a difference in the rate and the character of the respiration. Stimulation of the anterior surface of the lung root caused an increase in the pulse rate, irregularity in cardiac action, and a fall in the blood-pressure. These effects were most marked when

the electrode was applied to the sub-pleural tissue. Resection of the vagus in the neck just above the lung root abolished the respiratory reflex, but did not affect the cardiac reflex. When the stellate ganglion of the upper dorsal sympathetic chain was anesthetized, both reflexes remained unaffected. The local application of cocaine rendered both areas insensitive, but was dangerous because of absorption of the drug. The injection of a 1 per cent. solution of novocaine beneath the pleura covering the lung root abolished both respiratory and cardiovascular effects. The administration of atropine had no effect on these reflexes.

The vagus is an important sensory nerve and should be blocked with novocaine when operations are performed on the lungs. A swab soaked in 1 c.c. (16 minims) of cocaine is innocuous and will at least protect against cardiovascular disturbances.

## SYPHILOLOGY

By CARROLL SPAULDING WRIGHT, B.S., M.D.

**Introduction.**—The question of adequate treatment has been given increasing attention during the past few years by investigators and clinicians specializing in syphilology. A wide divergence of opinion exists, however. The Health Organization of the League of Nations finally has petitioned to make some authoritative recommendation, which resulted in the following statement:

1. Treatment should be recommended as early as possible in the seronegative primary stage.

2. Prior to any form of treatment there should be an adequate physical examination of the patient to determine the absence or otherwise of any indication for caution in respect to dosage.

3. Strict supervision of the patient at all times, especially with reference to mucous membranes, skin, kidneys and liver, is desirable.

4. Clinical and serological check up should be continued for never less than 3 years, and if possible, up to 5 years.

5. Adequate examination of the spinal fluid before dismissal from observation certainly is necessary.

6. In giving the actual treatment, the following measures are essential: (a) to use a comparatively heavy individual dosage of the arsenobenzine and of the bismuth or mercurial compounds, the doses being administered in comparatively rapid succession, particularly at the outset; (b) to maintain a persistent

attack on the disease, avoiding intervals of length as to afford the parasite an opportunity of recovering; (c) to administer approximately as much treatment to primary as to secondary cases.

7. Intermittent treatment is still in question. In general, the continuous form of treatment has been recommended by many observers but the final decision as to the relative value of intermittent or continuous treatment cannot yet be given.

***Etiology and Pathogenesis.***—EVIDENCE FROM DISEASED BONE.—During four centuries men have argued as to the place where syphilis originated. Controversy and polemic over the interpretation of old documents do not seem to have settled the question. But the study of ancient and diseased bones furnishes another method for attacking the problem, for the typical syphilitic skull gives a nearly certain means of diagnosis. Favorable specimens of long bones are also valuable, though not quite so convincing as the skull, since roentgenograms of long bones with chronic osteoperiostitis and yaws are sometimes much like those of syphilitic long bones. There is a better chance for determining the antiquity of syphilis through the examination of ancient bones than is the case with any other infection. There is the further advantage that the actual lesions of the disease are preserved in museums, where they may be seen by any person interested. It is not necessary to wrestle with anachronisms and with descriptions in archaic terms, in medieval Latin or in other foreign languages.

For this reason, H. V. Williams (Arch. Dermat. and Syph. 33:783 (May) 1936) devoted several years to examining the evidence to be found in ancient diseased bones. In 1932 he described 5 lots of bones that, on the authority of leading archeologists, were

of pre-Columbian age and that presented lesions indistinguishable from those produced by syphilis. To these may now be added 3 other groups of specimens, also stated to be pre-Columbian and having lesions similar to those produced by syphilis, one from Mexico, and one each from Alabama and Illinois in the United States. The specimens of Moodie from Arizona are probably syphilitic, but precise data to prove the antiquity of his specimens are not obtainable.

**EXTRAGENITAL CHANCRES.**—The history of extragenital chancres is almost as old as the history of the disease itself. The early writers were familiar with the prevalence of pox which followed the operations of scarification, cupping, venesection, vaccination, circumcision and tattooing as well as the ministrations of the midwife and wet-nurse. Paracelsus wrote about instruments as a medium of contagion. These historical data are gathered from Scheuer's monograph by N. Tobias (Am. J. Syph., Gonorr. and Ven. Dis. 20:266 (May) 1936).

Today local epidemics may be observed in families or small groups, but in the fifteenth and sixteen centuries extensive epidemics were not uncommon, the innocent victims numbering hundreds. The public bath, the barber, the midwife, the wet-nurse and the careless personal habits of the populace all were a menace to the public health.

With the spread of the science of sanitation, a rise in the economic level of society, and the discovery of arspenamine, extragenital infection, especially through innocent sources, has decreased considerably. This is particularly true in America and England.

Extragenital infections, according to Tobias, are more serious to the patient and his contacts than genital lesions for the following reasons:

1. He is usually unaware of the nature of the sore.

2. He applies home remedies for a week or longer until the occurrence of adenopathy or the secondary eruption frightens him into seeking medical consultation.

3. He may innocently infect others during this period.

4. If exposed to syphilis during sex contact, he may practice adequate genital prophylaxis, but neglect the other parts of the body.

Even when observing an extragenital chancre, the physician may fail to diagnose it for the following reasons:

1. A negative, false, or irrelevant history.

2. The unusual location of the lesion.

3. The absence of "textbook" characteristics, especially cartilaginous induration.

4. The presence of secondary infection may mask the picture.

5. The irritation from local treatment, and the absence of color values from the use of mercurochrome or silver nitrate may complicate the picture.

6. Extragenital chancres are usually much larger and much more inflammatory than the genital variety.

7. The physician thinks of syphilis last instead of first.

Fortunately the *Treponema pallidum* is an anærobe; otherwise, very few individuals would escape the disease. However, the organisms will live on the moist rim of a glass of water for 30 minutes. They are viable in fresh autopsy material and in the macerated syphilitic fetus for about 26 hours. In moist dressings applied to condylomata and other infectious lesions, they may be active up to 24 hours before desiccation kills them. They are quickly killed by the application of soap and water, as shown by Reasoner's experiments.

From the diagnostic standpoint, extragenital lesions are often a test of the examiner's skill and experience. Such conditions as epithelioma, furuncle, herpes, Vincent's disease, tularemia, tuberculosis cutis, and chancroidal ulcers must be excluded by dark-field examinations, observation, Wassermann follow-up, and, as a last resort, therapeutic tests.

Any accessible part of the body may serve as a site of inoculation for the *Treponema pallidum*. The ratio of infections to exposures depends upon the site, method of inoculation, duration of exposure to infected material, viability of spirochetes and character of prophylaxis. For practical purposes the sources of infection may be tabulated as follows:

1. Syphilis *d'embleé*—needle pricks, vaccination, tattooing, transfusions, dental extractions.

2. Syphilis *insontium* (innocent)—kissing, mouth to mouth insufflation, fighting, bites, cuts (razors, etc.).

3. Intermediate contagion—pipes, drinking glasses, eating utensils, musical instruments, razors, styptic pencils, toothpicks, combs, telephones, pencils, dressings, towels, surgical and dental instruments, douche nozzles, handkerchiefs (to remove foreign bodies in the eye), saliva (to stop bleeding).

4. Unnatural sexual practices—cunnilingus, fellatio, sodomy.

5. Occupational—physicians (gynecologists, obstetricians, pathologists, laryngologists), dentists, nurses, midwives.

6. Ritual—circumcision, axillary coitus (certain South African tribes).

7. Voluntary infection—to escape military service.

8. Superstition—belief among the ignorant, of Southern European countries especially, that contact with a virgin will cure venereal disease.

It is not true that syphilis acquired *via* the extragenital route runs a more malignant course or is more resistant to treatment. For many years it was believed that cerebral syphilis would follow in the wake of head chancres. Finger lesions were also considered to usher in a malignant form of syphilis. Personal experience has shown that the prognosis depends on early diagnosis and the institution of proper and prolonged treatment. Not one patient in the series observed has developed neurosyphilis to the knowledge of the writer. Nerve involvement, however, probably occurs with the same frequency as in genital lesions. In a large series of cases Dujardin has shown that extragenital syphilis shows no special resistance to treatment, and that symptoms referable to the central nervous system occur no earlier nor are they more common than in the usual type of infection. Standard minimum treatment instituted as soon as the diagnosis is made plus a coöperative patient offers a favorable prognosis and possible arrest of the disease.

**Diagnosis.**—**VALUE OF KLINE EXCLUSION TEST IN SERODIAGNOSIS.**—The United States Public Health Service in coöperation with the American Society of Clinical Pathologists devised an evaluation plan to appraise the various modifications of the complement fixation methods and flocculation tests developed and used in the United States for the serodiagnosis of syphilis. In order to determine the relative efficiency of these tests, the serologists who originally described the methods were permitted to perform their own tests. Those who described more than one test performed only one test in their own laboratory and delegated to another serologist, in a different city, the performance of the second. Rein, who collaborated with B. S. Kline in the development of the spinal fluid slide tests, performed the

exclusion slide test with spinal fluid and was delegated by Kline to perform the exclusion heated serum slide test.

The preliminary report of this study by C. R. Rein (*Am. J. Syph., Gonorr. and Ven. Dis.* 20:515, 1936) presents the evaluation of blood tests on 415 syphilitic and 152 normal, presumably nonsyphilitic, individuals. Also included for evaluation were presumably nonsyphilitic patients in special disease groups, such as tuberculosis, malignancy, fever, and pregnancy, and also blood specimens taken from normal nonsyphilitic women during menstruation and in the intermenstrual period. This increases the number of controls from 152 to 468 presumably nonsyphilitic persons who may be used to evaluate the specificity of each test.

At the most recent League of Nations Conference on the serodiagnosis of syphilis (Montevideo, 1930), an arbitrary standard was set up, dividing the serologic tests into 2 groups, depending on their degree of specificity. *Group A* included all methods giving less than 1 per cent. nonspecific reactions, while *Group B* included all methods giving more than 1 per cent. nonspecific reactions.

In the evaluation plan for the serodiagnosis of syphilis, the *Kline exclusion heated serum test* was the most sensitive of all tests in Group A (less than 1 per cent. false positive reactions in 468 presumably nonsyphilitic persons). By means of this test more persons with primary and latent syphilis (with varying amounts of treatment) were detected than by any other test (in Group A). This is particularly important in the control of syphilis, especially in outpatient departments and clinics and immediately before transfusions to prevent the transmission of syphilis.

As a secondary consideration, the low cost of materials and the rapidity and

ease of performance of the *slide tests* deserve the highest regard.

**IDE TEST.**—A simple new color test for syphilis has been reported by S. Ide and T. Ide (J. Lab. and Clin. Med. 21:1190 (Aug.) 1936). It requires only a microscope, special concave slides, the patient's blood or spinal fluid, 3.5 per cent. and 2.5 per cent. sodium chloride solutions for dilution purposes, and the Ide antigen. It is claimed that any physician can perform it in a few minutes in his own office. The Ide antigen is made of an extract of beef heart to which is added cholesterin, gum benzoin, crystal violet and azure II. The antigen is purplish-blue in color. The Ide test is positive for syphilis when, after a mixture of blood (diluted) and diluted antigen, purplish-blue granules or clumps appear among the red corpuscles examined under the microscope. In strongly positive cases the purplish clumps are visible to the naked eye. In negative reactions, only red blood cells can be seen.

**Prognosis.**—Theoretically and practically, syphilis is curable, but it is impossible to decide when the last spirochete has been eradicated in the individual patient. This question is nevertheless of grave moment to the community, to the infected person, and to the physician. J. E. Klein (Arch. Dermat. and Syph. 33:1055 (June) 1936) discusses the question of the curability of syphilis. Under modern conditions clinical and serologic "cure" is readily obtained in most instances. Radical biologic cure with complete destruction of the last spirochete is a therapeutic ideal which probably is attained frequently when intensive and continuous therapy is used during the early stages of the disease, especially in patients with primary syphilis, whose serologic reactions are negative. At present there is no reliable test for the

determination of the presence or absence of the spirochetes in the human body. The various serologic tests merely indicate a reaction on the part of the body against the spirochete. When these tests are negative there is no proof that the spirochete is not present in a state of latency.

There is a tendency to relapse after any plan of antisyphilitic therapy. Stokes and his associates have reported the incidence of cutaneous and mucous relapses as 9.6 per cent. in patients with an early stage of syphilis who received treatment with arsphenamine and as 3.6 per cent. after the use of arsphenamine and a bismuth preparation. Persistently positive Wassermann reactions were recorded in 6.6 per cent. of patients with primary and secondary syphilis and in 22 per cent. of those with latent, late and hereditary syphilis. Latency is a peculiar characteristic of the infection. It has been demonstrated at necropsy that a patient without clinical symptoms and with a negative serologic reaction may harbor intact spirochetes.

Certain modern concepts of syphilitic infection may help to dispel some of the complacency which has settled around this question. It is now realized that syphilis is a chronic infection in which the invasion by spirochetes becomes generalized early (long before the chancre appears) and that the infection runs a prolonged and varied course, with a tendency to relapse. Individual variations occur according to the constitutional reaction of the patient to the invader.

Success of treatment depends not on the serologic reaction, nor on a fixed scheme of treatment, but rather on the response of the constitution in the individual patient. There are constitutional differences in morphologic characteristics, function and even immunity which induce variations in response to the

spirochete and to the treatment. A suggestive investigation in this direction was made by Nishiwara (Bull. Soc. japon de syph. 12:2, 1935), who expressed the opinion that there may be a relationship between blood grouping and predisposition to disease. He found that the Wassermann reaction became negative with treatment in a higher percentage of patients whose blood belonged to group O or A than in those with blood of group B or A B. The physician who is aware of the importance of constitution as a factor in syphilis will treat the patient, not the spirochete or the serologic reaction.

In patients with *latent* syphilis the serologic reaction may remain positive in spite of maximal treatment. In other patients the reaction becomes negative promptly but the infection may continue. Chatschaturjan extirpated a lymph node from a syphilitic patient who had received 6 courses of treatment and presented no symptoms and had negative serologic reactions. On scrotal inoculation of a rabbit with this material, a typical chancre developed. In the state of latency there is a balance between the invasive powers of the parasite and the immune reactions of the body.

The incidence of *relapse* in spite of vigorous therapy, *latency* and *resistance to treatment* may be due to one or more of the following factors suggested by Ingraham: (1) A few of the parasites acquire tolerance for drugs; (2) the spirochetes are situated where a drug does not reach them; (3) the defensive powers of the host are defective; (4) the spirochete passes through a life cycle in which certain forms are resistant to drugs.

One must be content for the present to regard the spirochete as the sole cause of all the morbid changes associated with syphilis. When the early generalization of the infection, the ten-

dency to relapse, the uncertainties of modern "specific" therapy, the existence of latent and anergic infection, and the little understood immunology of syphilis are taken into consideration, a cautious, conservative and skeptical attitude as to the complete biologic cure of the infection seems justified.

It is more accurate to speak of "arrest" than of "cure"; at least this attitude might discourage a too prevalent optimism and complacency. It is therefore illogical to set a time limit, such as from 3 to 5 years, after which a patient may marry presumably with assurance of safety. From an ideal eugenic standpoint the syphilitic individual is undesirable *marriage* material. Should a syphilitic person marry and have progeny? If he insists on his biologic rights, tragedy is always possible, even with all the advantages of the highly developed modern treatment. A perusal of the best texts of modern syphilographers since 1910 indicates a tendency to prolong the duration of treatment and medical supervision of the syphilitic candidate for marriage. They recommend continuous treatment until the disease is clinically and serologically "cured," and then a life-time of medical supervision. The course of syphilis is unpredictable even by the most skilled physician. Since the physician can at no time assure the patient that his body is free from spirochetes, is it safe at any time to assure the syphilitic man that he may marry without endangering his wife and offspring? At best there may be offered a prospect of a reasonable span of life with a minimum of complications and assurance of arresting the infection if it is properly treated in time.

As concerns scientific medicine *versus* syphilis, the ancient struggle continues, with the hope that more profound studies in the biochemistry of the spirochete

and more basic researches in immunology and chemotherapy may some day bring the realization of Ehrlich's *therapia sterilisans magna* for this stubborn infection.

**Prophylaxis.**—Utilizing the rabbit as an experimental animal, J. F. Mahoney (Mil. Surgeon 78:351 (May) 1936) subjected the matter of prophylaxis in syphilis to critical analysis. In order to simulate as closely as possible the conditions of natural transmission of the disease, the contact method of transfer was employed. Carefully avoiding trauma, a cotton pledget saturated with a dark-field positive emulsion from a testicular syphiloma was packed into the preputial sac of male rabbits and held there by clamping the surrounding fur. Confusion with spontaneous spirochetosis of the rabbit was avoided, as far as possible, by a 30-day preliminary period of observation before the animals were utilized; all doubtful "takes" were clarified by gland transfer, and apparent failures were similarly verified.

The first series of experiments sought to determine the penetration time of the organism. Animals were exposed for periods of 1, 2 and 3 hours and were killed, and the penis was sectioned and stained for *T. pallidum*. At the end of an hour the organisms were found only loosely on the surface; by the second hour they were to be found in the deeper folds of the mucosa; but by the third hour they were to be found having penetrated the surface and lying within the tissues. Not surprisingly, the cells penetrated were always cuboidal, never squamous epithelium. Approaching the matter from another angle, Mahoney tried the effect of drastic antiseptics. Groups of rabbits were exposed for differing periods, which increased by half-hourly increments from 1 to 4 hours, following which the penis was thoroughly extruded to stretch out the

mucosal folds, vigorously scrubbed with soap and water, and then treated with tincture of iodine, alcohol, and ether. Up to and including the group exposed for 2½ hours no animal developed syphilis; 1 of 3 rabbits exposed for 3 hours developed the disease; and two-thirds of those exposed for 3½ and 4 hours, respectively, became infected. A parallel series treated with soap and water only were almost as well protected. Mahoney concludes, therefore, that from 2 to 2½ hours after exposure the organisms are still upon the surface and are vulnerable to direct local attack; after that period they have penetrated the tissues and infection has begun.

A standardized technic was adopted for studying the prophylactic effects of **mercury**; each animal was exposed for 1 hour, and irrespective of time or location of administration, each mercury-treated animal received 4 Gm. (1 dram) of 33 per cent. **calomel ointment**. This was sufficient to produce toxic symptoms. In the first series, calomel ointment was rubbed into the preputial sac before exposure, and none became infected, whereas all of the controls and all of a group in which a vaseline-lanolin ointment had been rubbed into the preputial sac developed syphilis. When the calomel ointment was applied to the preputial sac immediately after exposure, only 1 animal of 10 developed syphilis and this was a symptomless infection, and of great interest is the fact that only 3 animals of 10 became infected when the ointment was applied to the back immediately after exposure.

In a second series, all animals were protected by application of the ointment to the preputial sac after exposure, and only 1 of 10 of the group in which the ointment was rubbed into the back became infected. This series, however, is less satisfactory, because only 3 of 5 controls were positive. Smaller series

with longer exposure times gave similar results.

The author concludes, therefore, that the prophylactic effect of calomel ointment is due in part, at least, to a systemic spirocheticidal action, and emphasizes that there are two phases in prophylaxis which must be considered: "The first concerns that period of time in which the invading organisms occupy a vulnerable position upon the surface of the exposed area and may be influenced by antiseptic agents applied directly to that area. The second phase beginning from 2 to 3 hours after exposure must concern itself with systemic spirocheticidal therapy and would seem to bring up the question of the effective dosage of the agency used for this particular purpose."

The discussion on individual prophylaxis of syphilis at the French Congress for the prophylaxis of syphilis brought forth some interesting facts (Prophylax. antiven. 8:212 (Apr.) 1936). M. Pinard in opening stated that the use of prophylactic ointment had failed in the French Army, possibly because it was not used or not properly applied. More radical prophylactic methods cannot be considered to be free of danger. Pinard stated that he was aware of some deaths that had resulted from prophylactic treatment by the use of **pentavalent arsenic compounds** given by mouth. He had known severe mercurial dermatitis to result from the use of **calomel ointment** before and after coitus. Laurent stated that for an extended period of time he employed injections of an arsenical as a prophylactic in individuals known to be exposed to syphilis. Finally an officer with a primary lesion reported that he had had coitus with his fiancée the night previous. In spite of 2 intravenous injections of neoarsphenamine, the first given immediately, the girl developed a primary lesion, causing Laurent to lose faith in

this method of prophylaxis. Sicard de Planzoles and Spillman believed that the prophylaxis of syphilis depended upon education of the public in regard to prophylaxis, morals, and sanitation.

In the same journal Levaditi recommended the administration of **bismuth** to prostitutes who are constantly exposed to infection, to give them long continued protection. To achieve this protection the bismuth content of the organs must be kept at a constant level. Some had received bismuth as a prophylactic for as long as 9 years.

J. W. Bass (Texas State J. Med. 31:745 (Apr.) 1936), in this country, has recommended the following methods for the control and prevention of syphilis. (1) Elevation of morals; (2) suppression or control of commercialized prostitution; (3) venereal prophylaxis; (4) early diagnosis and treatment; (5) epidemiologic investigation of all cases for source and contact. The last two offer the best chance of immediate results.

**Treatment.**—**BISMUTH OR MERCURY WITH ARSPHENAMINE IN EARLY SYPHILIS.**—On the basis of observations and studies by A. B. Cannon and J. Robertson (J. A. M. A. 106:2133 (June 20) 1936) neither **bismuth** nor **mercury** appears to have such a decided advantage over the other as much strongly partisan testimony would lead one to believe. While in their comparative studies of the **arsphenamines**, arsphenamine proved to be almost uniformly superior to neoarsphenamine, and silver arsphenamine, by every criterion applied, no such clear-cut superiority could be discerned in the performance of either of the heavy metals. Spirochetes disappeared from primary lesions and the lesions themselves healed more promptly under bismuth than under mercury, but a positive Wassermann reaction reversed earlier under mercury



in the primary stage; in fact, one primary patient achieved a negative Wassermann reaction in 23 days under mercuric salicylate alone (5 injections) while his chancre was still unhealed and spirochetes were still present in the chancre fluid. In secondary syphilis, however, the situation was reversed: mercury gave slightly better results than bismuth in the healing of eruptions, condylomas and mucous patches, but mercury-treated cases were considerably slower in becoming Wassermann negative (they were at a disadvantage, however, in that the patients received preponderantly neoarsphenamine for their arsphenamine). Again, there were more than twice as many patients serologically resistant to mercury as to bismuth, but more relapses occurred under bismuth.

Among patients with early syphilis who completed the required first year of regular treatment, there was a larger proportion of satisfactory outcomes in the mercury group than in the bismuth group. The only clinical relapse occurred in a patient treated with bismo-cymol and silver arsphenamine, but the total number of injections received was below the optimum recommended. The only patient who showed a positive spinal fluid after completing a year of regular treatment received mercuric salicylate, silver arsphenamine and arsphenamine in but half the recommended dosage.

In the matter of complications that could be definitely attributed to the heavy metals alone, bismuth was responsible for only half as many as mercury; while of delayed systemic reactions such as dermatitis, jaundice and neuritis, in which both the arsphenamine and the heavy metal may be presumed to have had a part, the mercury group contributed only a little more than half as many cases as the bismuth group.

Thus the differences are not easily weighed and measured, and such differ-

ences as appear when the intramuscular injections are given alone, or preceding the first arsphenamine course, tend to become obliterated when an active arsphenamine preparation accompanies the heavy metal from the start. Facts uncovered in the present study suggest that:

1. The salts of both metals have an important place in the antisiphilic armamentarium. The various preparations selected—both of bismuth and of mercury—appear to have justified themselves in all cases examined in which the treatment was regular and the dosage adequate; but neither metal can compensate for the disadvantage of using an inferior arsphenamine preparation.

2. Mercury gives more brilliant but less uniform results than bismuth, so that in robust patients with a healthy excretory mechanism the body's natural defenses are perhaps more effectively stimulated by the mercurials. For patients less vigorous and for those who do not respond well to mercury preparation, bismuth offers a valuable substitute.

3. Arsphenamine can be counted on to deliver the strongest initial attack against *Spirochaeta pallida* and acts to best advantage when reinforced by one of the heavy metals; but if for any reason an arsphenamine is contraindicated, bismuth will probably give the better performance alone.

4. For those who would minimize the chances of ill-effects and for those who hold that the parasite may become drug-fast, alternating the two metals offers an obvious advantage.

ORAL ADMINISTRATION OF BISMUTH.—The recognized method of administering bismuth today is the intramuscular injection. Preliminary work has established the fact that bismuth given intravenously demonstrates too high a toxicity to be safe for administration in the treatment of syphilis. The oral administration, however, has been investigated.

The failure of the earliest experiments discouraged further attempts to administer the drug by mouth. Kolmer, in a *paper reviewed last year* outlined a number of indications for the oral administration of bismuth. In 1934, Serefis and Mulzer published a series of papers on the absorption of bismuth from the gastrointestinal tract. In a detailed report Serefis pointed out the fact that bismuth intoxications have been obscured following the oral administration of bismuth salts and this is proof that an occasional extensive absorption of bismuth takes place from the gastrointestinal tract. The rate of bismuth absorption in experimental animals following peroral administration has been recently studied by Clarke and Marsh (J. Pharmacol. and Exper. Therap. 57: 399 (Aug.) 1936). Three bismuth compounds were used—**sodium bismuth tartrate** with a metallic bismuth content of 72.7 per cent.; **potassium bismuth tartrate** with a metallic bismuth content of 65 per cent.; and **bismuth oxychloride** with a metallic bismuth content of 80.1 per cent. The following are their conclusions:

"The free acidity and pH of the gastrointestinal tract of the guinea-pig shows a sufficient similarity to the human tract to suspect that comparable results may be obtained in the human. This assumption, however, must be substantiated by further experimental work.

"Bismuth in the form of potassium bismuth tartrate, sodium bismuth tartrate and bismuth oxychloride, when administered perorally, is deposited in the liver, kidney and spleen of experimental animals.

"The highest concentration of any of these substances in the liver occurs at the end of a 24-hour period.

"The highest concentration of any of these substances in the spleen occurs at the end of a 24-hour period.

"The highest concentration of these bismuth preparations in the kidney occurs between the 12- and 48-hour period.

"Bismuth administered to pregnant pigs was found in detectable amounts in the fetal livers and placenta but not in the fetal kidneys."

The authors felt that the results of this experiment were of sufficient importance to warrant the continued experimentation with the peroral administration of soluble bismuth compounds.

The final preparation employed in the investigations of Serefis and Mulzer was called **bismutrate** and is said to contain the following ingredients.

|   |  |        |
|---|--|--------|
| <i>Complex amino-acid bismuth salt of oxytricarballic acid (bismuth chloride combined with glycerin, sodium citrate and liver extract).....</i> |  | 67.14% |
| <i>Sacch. Alb. ....</i>   |  | 25.60% |
| <i>Talcum ....</i>  |  | 3.30%  |
| <i>Stearic acid ....</i>  |  | 0.65%  |
| <i>Oleum anisi ....</i>   |  | 0.01%  |
| <i>Succh. glycyrrh. ....</i>  |  | 3.30%  |

Bismutrate is supplied in large tablets of light brownish color, each weighing 5 Gm. (1¼ drams) and containing 0.2 Gm. (1½ grains) of metallic bismuth. The tablets are not easily soluble in cold water, but when crushed may be brought into a uniform chalky, aqueous suspension of agreeable taste, resembling that of licorice. The tablets are more readily soluble in hot water.

Employing this preparation, C. R. Rein and M. B. Sulzberger (Am. J. Syph. Gonr. and Ven. Dis. 20:124 (Mar.) 1936) carried out the following experiments:

Fifteen adult male gray chinchilla rabbits weighing approximately 2500 grams each were used. These were inoculated on March 21, 1935, with an established and proved virulent experimental strain of *Treponema pallidum*. The inoculations were performed bilaterally, both in the scrotum and testes.

For the purposes of the experiment, the animals were divided into 4 groups as follows:

*Group 1: Prophylaxis Plus Treatment.*—Rabbits 64 and 67 received bismutrate on each of 3 successive days immediately prior to inoculation and beginning 42 days after inoculation.

*Group 2: Prophylaxis Plus Primary Abortion.*—Rabbits 62, 65, and 66 each received bismutrate on 3 successive days immediately prior to inoculation and on 4 days immediately after inoculation.

*Group 3: Secondary Abortion.*—Rabbits 51, 52, and 53 received bismutrate beginning 42 days after inoculation (12 days after the appearance of the primary lesion). Treatments were given approximately 3 times weekly during a period of 39 days (a total of 17 treatments per animal).

*Group 4: Positive Controls.*—Rabbits 50, 58, and 68, positive controls, were infected but received no bismutrate.

Each treatment consisted of the administration of a suspension containing one 5 Gm. ( $1\frac{1}{4}$  drams) tablet of bismutrate (200 mg.— $1\frac{1}{2}$  grains—of metallic bismuth) in approximately 10 c.c. ( $2\frac{1}{2}$  drams) of distilled water. The suspension was introduced into the stomach through a No. 12 F. rubber catheter. This tube was passed through the oral cavity and esophagus into the stomach and the suspension injected by means of a syringe.

Typical chancres appeared only in the animals of Groups 1, 3 and 4. The animals of Group 2 (*i. e.*, those receiving a combination of prophylaxis and primary abortive treatment) at no time developed chancres or any other clinical or serologic manifestations of syphilis. In those animals in which chancres developed, dark-field examinations were performed with uniformly positive findings.

The authors suggest further clinical experimentation with bismutrate in the treatment, prophylaxis, and, perhaps, also in the primary abortion of human syphilis.

MODERN METHODS *vs.* ARTIFICIAL FEVER AND BISMUTH PREPARATIONS ORALLY.—The management of syphilis has evolved step by step from Ehrlich's original tenet of "*therapia magna sterilisans*" through abortive and intermittent treatment schemes, to the modern method of continuous treatment of early

syphilis. A continuous treatment régime was first advocated in this country by Keidel as early as 1916-1917, and simultaneously abroad by Almkvist, but almost two decades elapsed before the carefully controlled reports of the Co-operative Clinical Group and of the Health Organization of the League of Nations firmly established the superiority of this method over all others heretofore proposed. It is now known that the proper employment of modern treatment methods can produce a cure in practically 100 per cent. of patients with seronegative primary syphilis, and in 90 to 95 per cent. of those with seropositive primary or secondary syphilis. Such excellent results, obtained only after 30 years of controlled clinical evaluation, must not be jeopardized by untried alternate treatment methods.

P. D. Rosahn (J. Chemotherapy 13: 49 (July) 1936) points out that the substitution of continuous arsenical and heavy metal therapy by inadequately tested therapeutic measures is particularly hazardous in early syphilis, in view of the well-recognized fact that the ultimate prognosis is very largely determined in the first two years of the disease. Substitute proposals should receive the same long-time critical appraisal that was given the early arsenicals, before any degree of general acceptance is accorded them. Ehrlich himself foresaw this eventuality, for he writes, "If it were really possible to discover another drug which gave the same results in experiments on animals as '606,' then an extensive series of experiments on man must first be made before it could bring a proof of its superiority in this direction."

These remarks are particularly pertinent at the present time in view of two recently proposed measures for the treatment of syphilis. The first of these is by means of **artificial fever**, the second by

the oral administration of a new **bismuth** compound. So far as these two methods are employed in the treatment of late symptomatic syphilis, no great harm can be done, since the disease has already progressed to the point of producing pathological changes. But since the adequate treatment of syphilis lies more in the direction of prevention than in cure, it is in early syphilis that the great hazards of the proposed therapy rest. In the absence of prolonged follow-up observations of treated cases, the final outcome, which is the crucial criterion of an antisiphilitic measure, must be in doubt. Moreover, the treatment of early syphilis by means of artificial fever, or by an orally administered bismuth preparation, prevents a very definite public health hazard, since early infectious relapses are likely to occur. Simpson, for instance, observed mucocutaneous relapse in the large proportion of 2 of 6 patients with primary or early secondary syphilis who had been treated by fever induced with the Kettering hypertherm.

Simpson also subjected 26 patients with early syphilis to a **combined fever and chemotherapy** régime, and observed this group for from 6 months to 2½ years. No matter how favorable the response may have appeared, the group is obviously too small and the follow-up period too short to determine the ultimate effectiveness of any antisiphilitic measure. Yet the author believes that combined fever and chemotherapy may be of great value in early syphilis, and in a later report states that the evidence "strongly suggests that the greatest field of usefulness for artificial therapy combined with specific therapy will ultimately be in its application to the early manifestations of syphilis, with a view to prevention of the often disastrous ocular complications." In this connection it should be recalled that Kerl studied

the effectiveness of combined **malaria-induced-fever** and **arsphenamine** therapy in early syphilis. Patients received from 7 to 10 fever treatments preceded and followed by approximately 3 Gm. ( $\frac{3}{4}$  dram) of arsphenamine. Among 41 patients with seropositive primary syphilis so treated, relapses of all types were observed in 13 or 31.2 per cent., and clinical relapses in 8 or 19.5 per cent. The combined therapy was employed in treating 202 patients with early syphilis (1 to 2 years after infection), and 62 or 30.7 per cent. of this group developed recurrences of all types, of which 34 or 16.8 per cent. were clinical recurrences. The large number of relapses observed by Kerl should call for extreme caution in accepting combined fever and chemotherapy as a treatment measure in syphilis.

No objection can be made to the clinical trial of these newer methods, provided such trial is rigorously restricted to a few carefully selected, competent observers. Unless a conscientious effort is made to limit the distribution of the proposed procedures to accredited observers, they are very likely to be adopted by ignorant or unscrupulous individuals. It is a distinct possibility, and one which is fraught with danger, that the treatment of syphilis may thus fall into the hands of the corner druggist and the second-story electric treatment dispenser.

Aside from these considerations, one other factor should cause great concern among those legitimately interested in the treatment and public health aspects of syphilis. It has taken almost a generation to teach the layman that syphilis is a disease which calls for long-continued treatment and observation. To publicize the fact that syphilis can be treated by means of a mild drug taken by mouth or by a few electric treatments may result in the complete nullification

of years of educational effort. The recently proposed therapeutic agents should be conclusively shown, by carefully controlled clinical investigation on a representative large series of patients, observed over a sufficiently long period of time, to produce a smaller proportion of early infectious relapses and a larger proportion of cures than accepted modern methods. Unless and until such evidence is available, all efforts to secure the adoption of fever therapy or of orally administered bismuth preparations in general medical practice should be vigorously opposed.

**MAPHARSEN.**—The trivalent arsenical preparation meta-amino-para-hydroxy-phenylarsine oxide was originally studied by Ehrlich and Bertheim and later by Voegtlin and others and found to be relatively toxic. In 1934, A. L. Tatum and G. A. Cooper (*J. Pharmacol. and Exper. Therap.* 50:198 (Feb.) 1934) showed that this drug, which is now known as mapharsen, possesses therapeutic values against experimental syphilis and trypanosomiasis comparable to those of the arsphenamines. O. H. Foerster, R. L. McIntosh, L. M. Wieder, H. R. Foerster and G. A. Cooper (*Arch. Dermat. and Syph.* 32:868 (Dec.) 1935) found mapharsen to be a potent antisiphilitic agent and its effects in syphilitic patients approximately equal to those which are expected from arsphenamine.

The drug contains 29.02 per cent. of metallic arsenic. It is a dry, hygroscopic, stable powder, readily soluble in water. The solution is slightly acid and when exposed to the air and agitation for hours may gradually darken. Change of therapeutic effect is said not to occur within 6 to 8 hours.

The maximum tolerated intravenous dose of mapharsen for rats is stated by O. M. Gruhitz and R. S. Dixon and a group of associates (*Arch. Dermat.*

and *Syph.* 34:432 (Sept.) 1936) to be from 16 to 18 mg. per kilogram of body weight. They summarize an extension study of the use of mapharsen for syphilis by reporting on 4,841 cases of syphilis treated with a total of 75,589 injections. "The average initial dose for adult patients of both sexes was 0.04 Gm. ( $\frac{2}{3}$  grain). The subsequent maintenance dose for women was 0.04 Gm. ( $\frac{2}{3}$  grain) and for men 0.06 Gm. (1 grain). Treatment consisted of weekly injections of mapharsen for 8 weeks, followed by 8 weeks of treatment with heavy metal. The courses alternated for 1 year or over without a rest period until 3 courses of mapharsen and 3 courses of heavy metal were completed.

A time treatment course of mapharsen averaged between 0.98 Gm. (15 grains) and 1.38 Gm. (21 grains) of the drug. This amount of mapharsen contains only about one-tenth as much arsenic as a similar course of an arsphenamine. In a group of 4841 patients, receiving 75,589 injections, no severe complications or death occurred. No instance of hemorrhagic encephalitis, hemolytic anemia, jaundice, severe exfoliative dermatitis or severe nitritoid crises occurred. Moderately severe reactions necessitating discontinuation of treatment occurred 4.4 times per thousand injections. These reactions in preponderance were associated with gastrointestinal disturbance.

Spirochetes disappeared from moist lesions within from 24 to 48 hours after an initial dose of 0.04 Gm. ( $\frac{2}{3}$  grain). Lesions healed more readily than similar syphilitic lesions under neoarsphenamine therapy. No patient with early syphilis was encountered whose condition did not respond to mapharsen medication. In several instances early syphilis which did not respond to neoarsphenamine responded readily to mapharsen therapy. Reversal of serologic

reaction occurred under continuous treatment with mapharsen for 1 year in 100 per cent. of cases of seronegative syphilis, 92 per cent. of cases of seropositive primary syphilis and 97 per cent. of cases of secondary syphilis. With all methods of treatment of all types of early syphilis for 1 year of time treatment the reversal of serologic reaction occurred in 90 per cent. of cases. Serologic relapse in a period of probation of from 2 months to 2 years occurred in 14.9 per cent. of the cases. Involvement of the spinal fluid developed only under irregular treatment. With all methods of treatment cerebrospinal involvement developed in 8.2 per cent. of the cases.

Mapharsen in mass treatment of syphilis when used in conjunction with heavy metal appeared prompt in action; it caused no severe unfavorable reactions, and mild reactions were fewer than those produced by the arsphenamines. It caused prompt and sustained reversal of a positive reaction of the blood. Mapharsen was not found to possess cumulative retention in the body.

It is interesting to note that in 1934 Tatum and Cooper gave 1.66 as the therapeutic index of arsenoxide as against 1.11 for neoarsphenamine. In experimental trypanosomiasis the index for arsenoxide was given as 25, while various brands of neoarsphenamine ranged from 20 to 40. It was also noted by Tatum that primary lesions disappeared several days sooner with arsenoxide than with neoarsphenamine. On the basis of these findings, it was concluded by him that arsenoxide was superior to neoarsphenamine in experimental trypanosomiasis and rabbit syphilis, and that, therefore, a clinical trial was desirable in human syphilis.

A critical examination of the above results by G. W. Raiziss and M. Severac (Am. J. Syph. and Neurol. 19:473 (Oct.) 1935) revealed an important

discrepancy between the value of the therapeutic index for neoarsphenamine as given by Tatum and as determined by various other investigators. Tatum gives 1.11 as the value of the index for neoarsphenamine, while on the basis of existing literature, as, for instance, summarized in a paper by Voegtlin, values are obtained for this index ranging from 4 to 7.5. This difference arises from the fact that while Tatum obtains toxicity values for neoarsphenamine comparable with those of other investigators, his value of the minimum curative dose (180 mg. per kilogram of body weight) is several times larger than the generally accepted figure. Voegtlin, in the paper already referred to, concludes that the minimum curative dose of neoarsphenamine in rabbit syphilis is 0.040 Gm. (40 mg.) per kilogram of body weight, basing this statement on his own experiments as well as on a critical evaluation of existing literature. It is quite obvious that a drug possessing an index of 1.11 could not be safely used, for the maximum tolerated dose would be very nearly the same as the curative dose, and the margin of safety almost *nil*. This is certainly not true of neoarsphenamine, where an index of at least 5 is quite in accordance with clinical experience. In the case of arsenoxide, the index as given by Tatum, 1.66, is still too low to make the drug safe, for it corresponds to a maximum tolerated dose of 0.010 Gm. ( $\frac{1}{10}$  grain) against a minimum curative dose of 0.006 Gm. ( $\frac{1}{160}$  grain). The difference between the two is not very great, and in view of the approximate nature of these figures arising from experimental uncertainties, the margin of safety is again very narrow.

In view of the intrinsic importance of the question, however, concerning as it does the efficiency of the major weapons of syphilotherapy, Raiziss and Severac

performed a series of experiments having as their object a critical study of the therapeutic efficiency and toxicity of arsenoxide A and arsenoxide B as compared with neoarsphenamine, and summarized their findings as follows:

"1. The maximum tolerated dose for arsenoxide given intravenously to rats is 0.018 Gm. per kilogram of body weight; for neoarsphenamine, 0.400 Gm. per kilogram of body weight.

"2. The minimum trypanocidal dose of arsenoxide is 0.0025 Gm., of neoarsphenamine 0.020 Gm.; hence, the therapeutic index (trypanocidal) of arsenoxide is 7.2, of neoarsphenamine 20, which is almost three times greater.

"3. The maximum tolerated doses of arsenoxide and neoarsphenamine in rabbits (upon intravenous injections) are 0.011 Gm. and 0.200 Gm. respectively.

"4. The minimum curative doses of arsenoxide and neoarsphenamine in experimental rabbit syphilis are, respectively, 0.012 Gm. and 0.040 Gm. The therapeutic indices are, therefore, 0.92 and 5, respectively. Neoarsphenamine is about  $5\frac{1}{2}$  times as efficient as arsenoxide.

"5. On the basis of these findings, one is forced to conclude that neoarsphenamine is far superior to arsenoxide both in its trypanocidal and its spirocheticidal effect. In experimental rabbit syphilis the maximum tolerated dose and the minimum curative dose for arsenoxide are practically identical, which suggests that the clinical use of this drug in adequate curative doses might be fraught with considerable danger."

It is readily evident that there is a marked discrepancy between the opinions of different writers as to the comparative value of neoarsphenamine and arsenoxide and that further studies will be required to properly evaluate the latter. A recent report by G. V. Kulchar and C. W. Barnett (Am. J. Syph. Gonorr.

and Ven. Dis. 20:482 (Sept.) 1936) states that in 56 patients with primary and secondary syphilis, the healing of the lesions was more rapid than with neoarsphenamine but that serologic reversal was somewhat slower.

REST.—Very little consideration has been given to the effects of rest in the results of antisyphilitic treatment, according to M. E. Obermayer and S. W. Becker (Arch. Dermat. and Syph. 34: 57 (July) 1936), yet the distinct influence which antisyphilitic treatment has on a patient's general well-being must be apparent to every experienced syphilologist. The authors have endeavored to evaluate the various factors which might be responsible for both subjective and objective improvement in the majority of patients and for lack of improvement in the minority.

The general beneficial effect of antisyphilitic treatment is caused by the following factors:

1. *Specific Effect of Antisyphilitic Drugs.*—This needs no explanation. It is readily understood that elimination (*in toto* or in part) of a chronic infectious process will result in an improvement of the general well-being of the patient.

2. *Nonspecific Effect of Antisyphilitic Drugs.*—This seems to play a negligible rôle as far as compounds of mercury and bismuth are concerned but is a definite factor in the case of the arsenical compounds. Their tonic action—undoubtedly due to their arsenic content—form a welcome addition to the effect of treatment. This tonic action is most pronounced in patients treated with **tryparsamide**, in whom considerable gain in weight is to be expected. In addition, tryparsamide is a mild aphrodisiac, most welcome in raising the spirit of the discouraged and depressed tabetic patient.

### 3. *Effect of Nonspecific Treatment.*—

It has been realized for a long time that it is a serious mistake to treat syphilis merely chemically. Syphilis shows many parallels with tuberculosis, so close that even microscopic examination sometimes cannot differentiate the clinical manifestations of the two diseases; the continuous fight between the defense mechanism of the host and the virulence of the etiologic agent is common to both. It is now definitely recognized that resistance-building measures, especially rest, are necessary in the treatment of tuberculosis. This is just as important in the treatment of syphilis, in which the results of poor therapy are more remote and not as dramatic as in tuberculosis. The authors have found the combination of generalized **ultraviolet irradiation** and **injections of autogenous blood** a valuable aid in converting persons with a tendency to relapse into normally reacting patients.

4. *Patient's Habits and Ways of Living.*—Any one afflicted with a constitutional chronic infectious disease should live according to a certain regimen if he expects the full benefit of medical treatment. Patients with syphilis are no exception to this. Stokes has said: "Rest is one of the potent, and often life-saving factors in the general management of the syphilitic patient. More and more frequently in the recent literature one encounters the theory that loss of resistance to the disease and failure to make therapeutic headway against it are functions of the exhaustion of the defence mechanism, including presumably the reticulo-endothelial system and the antibody-forming agencies, a loss of function which may be recovered after rest." Normal sleeping hours, a nap after luncheon, reduction of mental and emotional strain and regular vacations, spent in the country, are essential additions to the specific treatment.

The **diet** presents another point of attention. Since constitutional syphilis is associated with marked consumption of proteins, the diet of the patient should be rich in calories and especially in proteins.

The study deals with the influence of the patient's habits and ways of living on the general beneficial effect derived from therapy. Data compiled by means of questionnaires, analyzed and given in tables, reveal the paramount beneficial influence of restful living on the subjective feeling of well-being, as well as on increase of weight on the part of syphilitic patients.

Physicians who treat syphilis should not treat the patient merely specifically but should utilize the value of decreased tension of the patient's life.

COMPLICATIONS OF TREATMENT.—*Dermatitis due to tryparsamide* is rare, according to S. S. Robinson (Arch. Dermat. and Syph. 34:251 (Aug.) 1936), who was able to collect only 12 cases from the literature. In case personally reported the eruption consisted of diffuse, ill-defined, erythematous, scaling, maculopapular lesions on the upper part of the thorax and especially in the axillæ. Patch tests with tryparsamide were positive on the involved skin, but gave negative results on the uninvolved areas. Seven and one-half grains (0.5 Gm.) of **calcium thiosulphate** were given intravenously and most of the lesions disappeared in one week.

H. M. Robinson and Kemp and Menninger believe that the fixed eruption due to tryparsamide does not contraindicate the further use of the drug. Treatment was continued in their cases without further complications.

It is interesting that because of the mild character of the eruption due to tryparsamide in the cases that have been described, usually the patient was not impressed sufficiently to inform the



physician of the reaction. As extensive exfoliative dermatitis has occasionally resulted from treatment with tryparsamide, it would be wise as a routine to examine all patients under treatment with the drug and question them regarding cutaneous lesions.

**TREATMENT-RESISTANT SYPHILIS.**—Although there is an apparent increase of treatment-resistant syphilis, particularly arsphenamine-resistant syphilis, in France and Germany, there is no such increase in the United States, according to H. Beerman (Am. J. Syph., Gonorr. and Ven. Dis. 20:165 (Mar.); 296 (May) 1936), who has studied the question exhaustively and gives the following summary. This is indicated by the paucity of cases reported and seen in large syphilis clinics over a period of 10 years. Nonetheless, the problem of treatment-resistant syphilis merits repeated study because of its seriousness.

The concept of treatment-resistant syphilis is variously defined. The essential criteria of treatment-resistant syphilis are: (a) persistence of lesions; (b) persistently positive blood serologic tests; and (c) persistence of spirochetes in spite of usually adequate treatment. Of these three, the persistence of *Spirocheta pallida* in the lesions is the most reliable criterion of treatment-resistance in human syphilis.

Based on clinical appearances, treatment-resistant syphilis can be divided into 4 major groups, using (a) arsphenamine resistance (*formes larvées, la demi-arséno-résistance*—Gougerot); (b) arsphenamine recurrences (*arséno-récidive*); (c) true arsphenamine resistance (*arséno-résistance caractérisée*); (d) arsphenamine activation or stimulation (*arséno-activation*—Nicolas, Lacasagne, Froment; *la stimulo-arséno-résistance ou réaction de résistance*—Gougerot and Fernet). These groups

are poorly defined and in reality represent only varying degrees of treatment resistance.

Treatment-resistant syphilis may manifest itself in any stage of a syphilitic infection and may affect any organ of the patient. The most characteristic lesions, however, occur in early syphilis and are usually cutaneous. These lesions are very often papulosquamous and psoriasiform and have characteristic localization, being distributed as a rule to the face, neck, penis, and upper extremities. At times the lesions may be typical syphilids, but precocious in their development.

A number of patients with treatment-resistant syphilis react poorly to the drug.

The blood serologic reactions in many patients with treatment-resistant syphilis differ from those of the average patient in that seronegative secondary syphilis is rare (about 1 per cent.), but in treatment-resistant syphilis the tendency to negative blood serologic reactions occurs about 5 times as often. Moore and Kemp noted that the positive blood serologic tests of a group of treatment-resistant patients tend to reverse readily under treatment.

The *diagnosis* of treatment-resistant syphilis depends largely upon a study of the clinical manifestations and the course of the disease. Recent studies of the changes in the leukocyte count of the blood before and after treatment is administered (leukocytic reaction of Gouin) suggest that it may be possible to predict resistance to a drug.

The *prevention* of treatment-resistant syphilis depends to a large degree on the adequate treatment of early syphilis.

The *management* of a fully established case of treatment-resistant syphilis is discussed. Various procedures may be employed. Among specific measures are included (a) changing the

preparation to another member of the same group, *e. g.*, from neoarsphenamine to arsphenamine (606); (b) changing the manufacturer's lot of the same preparation; (c) changing the manufacturer's brand of the same drug; (d) changing to another type of antisyphilitic agent, *e. g.*, from arsenicals to **bismuth salts, mercurials**, or minor antisyphilitic drugs, especially **gold**. Among nonspecific measures are included (a) **high caloric diet**; (b) **temporary suspension of antisyphilitic treatment**; (c) **elimination of other intercurrent systemic diseases**; (d) **shock therapy with milk, gonococcus vaccine autohemotherapy, sodium nucleinate, fever induced by malaria, sulphur preparations, vaccine, *e. g.*, typhoidparatyphoid**.

Treatment-resistant syphilis has been ascribed to 1 factor or the interaction of 3 factors: the host, the drug, and the spirochete. A review has been made of the evidence bearing on each of these factors. The consensus at present seems to regard the host as the factor most responsible for treatment-resistant syphilis. While a number of studies have indicated that under certain conditions *Spirocheta pallida* may be made to develop a certain degree of resistance to antisyphilitic drugs, no one up to the present has reported the transfer of *Spirocheta pallida* from a treatment-resistant syphilis in man to rabbits with preservation or demonstration of treatment-resistant characteristics in the rabbits.

An opportunity to study the part played by *Spirocheta pallida* in treatment-resistant syphilis was afforded by a patient with early syphilis whose primary and secondary lesions had been uninfluenced by a total of 5.4 Gm. ( $1\frac{1}{3}$  drams) of various arsenicals, but whose infection was later, after animal transfer, satisfactorily controlled by the

prolonged use of **bismuth salts** intramuscularly and nonspecific therapy in the form of **milk injections** intramuscularly.

In the experimental study (1) the characteristics of a recently isolated strain of *Spirocheta pallida* from this patient with treatment-resistant syphilis infection were observed; and (2) the effect of arsphenamine treatment on rabbits infected with this strain and rabbits infected with the Nichols strain of *Spirocheta pallida* was compared.

In these studies it was found that the incubation period of *Spirocheta pallida* isolated from the writer's patient was about the same as that of the Nichols strain. The new strain of organism possessed a high degree of infectivity for the rabbit in spite of being derived from a treated patient. Even the blood of the patient was infectious after 13 arsenical treatments. The lesions produced by these spirochetes in rabbits were inconspicuous and tended to rapid spontaneous involution (low reaction-inducing power). The strain of *Spirocheta pallida* has also a tendency to produce asymptomatic infection in the rabbit.

In experiments controlled by the use of a standard established strain of *Spirocheta pallida* (Nichols strain) and by the use of a lot of arsphenamine whose minimal sterilizing dose over a period of about 10 years has been 14 mg. per kilogram of body weight, it was found that 5 of 23 rabbits infected with the new strain were not "cured" by doses of 16 and 18 mg. of arsphenamine per kilogram of body weight. This observation on a fresh strain in the presumptively unfavorable environment of a recent transfer to animals certainly suggests that the strain of *Spirocheta pallida* isolated from the present case of treatment-resistant syphilis has intrinsic refractoriness toward the arsenicals.

This refractoriness, while undoubtedly more marked at the outset, still shows signs of persistence in the eighth animal passage.

**NEUROSYPHILIS.** — *Influence of Inadequate Treatment of Early Syphilis on Incidence.* — The fact that any group of neurosyphilitics contains a large percentage of patients who were inadequately treated for early syphilis fails to show that the incidence of neurosyphilis was increased by this type of treatment. It does show that inadequate treatment has failed to cure a chronic disease and, since the majority of patients with early syphilis receive inadequate treatment, it is not surprising to find that they comprise a large proportion of any group with late syphilis. J. E. Kemp and W. C. Menninger (Bull. Johns Hopkins Hosp. 58: 24 (Jan.) 1936) undertook a study to test the validity of the assumption which is accepted by many syphilologists that inadequate treatment for early syphilis increases the incidence of neurosyphilis and shortens the incubation period. It was the authors' opinion that irregular treatment cannot be said to increase the incidence of neurosyphilis unless it be shown that the percentage of neurosyphilis is less among patients who have had no treatment for early syphilis than it is among those who have been given inadequate or irregular treatment.

The material of this study consists of a review of 1500 consecutive admissions to a large syphilis clinic—680 cases being selected in which there was no doubt about the history of infection, its duration, and the amounts of treatment given during the first two years. All patients had spinal fluid examinations or clinical neurosyphilis sufficiently advanced to make this procedure unnecessary for diagnosis. Patients who gave a history of inadequate treatment for early syphilis and who had received desultory

treatment for late syphilis were not included unless the diagnosis of neurosyphilis had been established at the time treatment for late syphilis was begun, or unless it seemed certain that this treatment had not influenced the course of the disease.

A study of the 680 cases reveals: 253 had had no treatment, of these, 52.6 per cent. showed clinical or laboratory evidence of neurosyphilis; 226 had had early inadequate treatment, of these 43.4 per cent. showed evidence of neurosyphilis; 201 had had early adequate treatment, 16.9 per cent. of these showed evidence of neurosyphilis.

The duration of the incubation period of clinical neurosyphilis among 112 of the patients was as follows: Among those who had had no treatment, the average incubation period was 17.6 years; among patients who had been given early inadequate treatment the average incubation period was 11.6 years; among persons who received early adequate treatment, the average incubation period was 11.4 years.

The sex distribution is of interest. Of the total number of males (330), 147 had neurosyphilis; of the 350 females, 118 had neurosyphilis. With no treatment the incidence of neurosyphilis was only slightly higher in males than in females, but among those inadequately treated for early syphilis, neurosyphilis was 25.2 per cent. higher in males than in females.

#### **SYPHILIS IN PREGNANCY.**—

A report is made by H. W. Cole, L. J. Usilton, J. E. Moore, P. A. O'Leary, J. H. Stokes, W. J. Wile, T. Parran, Jr., and R. A. Vonderlehr (Ven. Dis. Inform. 17:39 (Feb.) 1936; J. A. M. A. 106:464 (Feb. 8) 1936) of the effect of treatment on the outcome of pregnancy in syphilitic women. The data show that congenital syphilis is practically a preventable disease. Its preven-

tion is dependent upon the routine, early and repeated use of the serologic blood test on every pregnant woman and upon adequate early treatment once the diagnosis of syphilis has been made.

A positive blood reaction during pregnancy is a serious matter to the fetus. Ten times as many syphilitic children were born when the syphilitic mother's blood was positive during pregnancy as when it was negative.

The pregnant syphilitic woman was found to tolerate antisyphilitic treatment as well as, or better than, the syphilitic woman who had not been pregnant since infection.

There is evidence that habitually aborting syphilitic women are capable of producing living, apparently nonsyphilitic children when given specific treatment throughout each pregnancy.

Many more nonsyphilitic living children were born when antisyphilitic treatment was begun before the fifth month of pregnancy than when therapy was delayed. This advantage was increased if the treatment during pregnancy was not only early but adequate, *i. e.*, at least 10, preferably 15, injections of arsenamine and appropriate heavy metal.

If an early syphilis appears late in pregnancy, some treatment begun at this period and continued up to termination of pregnancy, even though it is only a small amount, will be of value in the production of a living child. To those women with early syphilis who were treated after the fifth month of pregnancy only 7.6 per cent. of the children were born dead; whereas among a similar group of women with early syphilis to whom no treatment was administered during pregnancy the loss of life was 46 per cent.

Treatment during a preceding pregnancy is insufficient protection for the present pregnancy, even though the syphilitic woman has a negative blood

reaction. It is necessary to treat her throughout each pregnancy to insure a living nonsyphilitic infant.

The important factors in controlling clinical progression and relapse in the syphilitic woman are the stage of syphilis on beginning treatment and the amount of therapy administered, rather than the pregnancy. The possible exception is the apparent protection pregnancy affords the early syphilitic in avoiding an involvement of the central nervous system.

### CONGENITAL SYPHILIS.—

*Preventive Treatment.*—Four methods of preventing congenital syphilis are suggested by H. Gougerot (Prophylax. antivén. 8:14 (Jan.) 1936): (1) Preventing syphilitics from procreating children until their syphilis is cured; (2) giving a precautionary antisyphilitic treatment to married syphilitics before they procreate any children; (3) treating the future mother during her pregnancy; (4) treating infants born of syphilitic parents even when they appear to be normal. These four measures, if followed out strictly, will reduce congenital syphilis to a minimum.

It is generally agreed that the best treatment for the mother is **arsenobenzene**. The patient should be watched carefully for signs of intolerance. **Bismuth** is certainly less toxic than the arsenicals, but it is also less effective. It is indicated if the arsenicals are impossible or badly tolerated, and if the syphilis is old or very much attenuated, or if it is resistant to arsenic as shown by arsenic having little or no effect in previous pregnancies. Mercury is distinctly inferior to the other two drugs.

Several technics have been proposed for arsenic treatment. Some give short courses of **arsenobenzol**, for example, 4 injections of 0.15 to 0.6 Gm. ( $2\frac{1}{2}$  to 10 grains) followed by a month of rest

and then a repetition of the same series. Others give the same treatment as to the nonpregnant woman, beginning with small doses and increasing rapidly to the so-called normal dose of 0.015 mg. per kilogram of weight up to a total dose of 0.10 cg. per kilogram; that is for a patient weighing 60 kilograms doses of 0.15, 0.30, 0.45, 0.60, 0.75, and 0.90 Gm. ( $2\frac{1}{2}$ , 5,  $7\frac{1}{2}$ , 10,  $12\frac{1}{2}$ , and 15 grains).

Most obstetricians give intravenous injections but uteroplacental nitritoid crises may cause abortion. For this reason the author prefers intramuscular injections for, while they are painful, they give the maximum degree of security. If the patient prefers intravenous injections he gives them, but keeps careful watch and on the slightest signs of intolerance changes to intramuscular injections. To counteract the possible bad effects of the injections, the drug may be dissolved in 5 to 10 c.c. ( $1\frac{1}{4}$  to  $2\frac{1}{2}$  drams) of 10 per cent. cesium eosinate or 5 to 10 c.c. ( $1\frac{1}{4}$  to  $2\frac{1}{2}$  drams) of an aqueous solution of sodium hyposulphite.

**Treatment.**—The use of acetarsone (stovarsol) as a therapeutic agent in the treatment of congenital syphilis is more than a decade old. In 1924, Duperie, Cadenaule and Clarac reported a child 2 months old suffering from congenital syphilis who was treated with acetarsone orally with excellent results. Since that time a large number of reports favorable to the oral use of this drug have appeared in the literature both in this country and abroad. In 1932 acetarsone was introduced into the congenital syphilis clinic of the Winnipeg Children's Hospital and recently A. M. Davidson and A. R. Birt (Canad. M. A. J. 34:33 (Jan.) 1936) has reported the results of its use in 51 cases. He reports that the results obtained have been much superior to those pro-

duced by the older methods of treatment. The decided increase in the percentage of cases cured is enough in itself, according to Davidson, to assure this drug a permanent place in the therapy of congenital syphilis. In addition, it offers the following advantages over other forms of treatment:

1. *Simplicity of Exhibition.*—The oral method is much superior to the intravenous or the intramuscular route in children, for obvious reasons.

2. *Regular Attendance at Clinic.*—Syphilis in all its forms can only be cured by regular treatment. In the pre-stovarsol series of cases there were many irregular attendants at clinic. The children who did attend regularly had to be forced by their parents or guardians. Since the introduction of stovarsol and the cessation of painful treatments there has been no difficulty in having the children attend the clinic regularly.

3. *Toxic Effects.*—There have been fewer toxic effects in this series than are usually found with arsphenamine and neoarsphenamine. Those that have been produced were readily controlled by dosage.

4. *Cost.*—Treatment is much cheaper than by other methods. The stovarsol costs less and there is no additional equipment necessary for administration.

Acetarsone tablets are 0.25 Gm. (4 grains) by weight and are readily divided into quarters. For infants the tablets are dissolved in water or in part of the milk feeding and given according to the following dosage:

*Dosage of Acetarsone*

$\frac{1}{4}$  tablet once a day for one week.

$\frac{1}{4}$  tablet twice a day for one week.

$\frac{1}{4}$  tablet three times a day for one week.

$\frac{1}{4}$  tablet four times a day for one week.

$\frac{1}{2}$  tablet three times a day for one week.

$\frac{1}{2}$  tablet four times a day for one week.

1 tablet twice a day for one week.

Total, 56 tablets (14 Gm.— $3\frac{3}{8}$  drams) in 49 days, followed by a 6 weeks' rest period.

J. B. Givan and G. Villa (Am. J. Syph., Gonorr. and Ven. Dis. 20:275 (May) 1936) used **acetarsone** intravenously in the treatment of congenital syphilis and found it to be a safe remedy. Furthermore, they found the Wassermann and Kahn tests to be favorably influenced in the majority of cases. No disturbances of vision were overlooked. It was found to be better tolerated than neoarsphenamine and

could be used in some cases showing intolerance to neoarsphenamine. Nauseating effects occurring immediately after administration of neoarsphenamine due to odor and taste of the drug were not noted in the same degree after acetarsone therapy. A series of 30 children with congenital syphilis, given a total of 463 injections of intravenous acetarsone, showed no untoward reaction requiring treatment or discontinuance of the drug.

# SURGERY

Edited by W. WAYNE BABCOCK, A.M., M.D.

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## ABDOMINAL SURGERY

By JAMES NORMAN COOMBS, M.D., and FRANCIS L. ZABOROWSKI, M.D.

**INTRODUCTION.**—During the past few years much progress has been made in the field of abdominal surgery. Some of the more important advances are briefly referred to in the following review of recent literature.

The value of an accurate x-ray examination in the *diagnosis of abdominal tumors*, to show whether the tumor is within or without the gastrointestinal tract, has been important in almost every case. Following such examination, the use of physical signs and differential tests usually lead to an accurate diagnosis. Difficulty often arises in the diagnosis of the large *cystic tumors of the kidney* and *tumors of the ovary* when such tumors fill the abdomen and extend to the liver. *Lymphogranuloma* and *lymphosarcoma* of the *retroperitoneal glands* may yield decisive findings in differential diagnoses by blood studies, swellings of other glands and tumor of the spleen.

Very careful and thorough examination is always necessary in passing judgment on painful *abdominal conditions* in *children*. Due consideration must be given to posture of the child, the position of the legs, the type of respiration, the configuration and surface relief of the abdomen. Changes in abdominal respiration are of great diagnostic importance. Tenderness to pressure should never be determined by questioning. Rectal examination should always be made. With due regard to appendicitis,

intussusception and the other common intraabdominal conditions causing pain, concern must be given to nonabdominal conditions producing abdominal pain. Important causes of such pain are pneumonia, pleurisy, pericarditis and myocarditis. Abdominal pain may occur also in affections of the nasopharynx, palatine tonsils, grippal diseases, scarlet fever and measles.

In *recognizing the patient who will not be helped by abdominal operation*, the diagnosis of functional disease should be made on the basis of a careful history and on the recognition of a well-known syndrome. When the diagnosis is not clear, careful exploration of the abdomen is required. It has been stated that a large proportion of interval "appendectomies" should have been "explorations." It is not advisable to operate on persons with conditions of doubtful pathogenicity, such as ptosis; or on persons who are psychopathic, hypersensitive, constitutionally inadequate, highly allergic or migrainous; or on persons who are on the verge of a nervous breakdown.

A clearer understanding of *disruption in abdominal wounds* may be obtained by considering intraabdominal variations in pressure in the postoperative state and the type of suturing material used. It is to be recognized that rupture of a wound is possible following the use of any type of suturing material and any type of closure, including the use of

retention sutures. The integrity of the tissues depends on many factors, such as wound infections, sepsis and constitutional diseases. In the presence of such factors, careful suturing, the more general use of a suitable nonabsorbable suture, such as noncorrosive steel alloy wire (Babcock) is suggested.

The modern surgical treatment of *peptic ulcer of the stomach and duodenum* is largely the treatment of the complications of ulcer, *i. e.*, perforation, bleeding, and obstructive phenomena. As a clinical test of malignancy, Pfeiffer and Levering recommend the plan of Lahey with certain reservations. Lahey hospitalizes all peptic ulcer cases for a period of 3 weeks under very careful treatment. If, after this study and treatment, the ulcer fails to show improvement, it is classed as intractable, and surgical measures are instituted whether or not cancer already exists.

Prompt measures to close perforation of ulcers with minimal surgery are outlined.

In *bleeding ulcer*, wisdom is shown in conservatism in its management. Surgical interference is indicated in bleeding from ulcers of the chronic callous type and when hemorrhage has been severe or repeated. **Gastroenterostomy** alone affords a high percentage of cures in duodenal ulcer where excision cannot be performed.

A simple method of *enterostomy* is described by Pfeiffer and Levering whereby a simple purse-string suture, which is first placed in the intestine in an isolated loop, is used. Through a small stab-wound in the center of this, the catheter or rubber tube is placed and the purse string tied. Another purse string is placed around the first suture and this is tied after the catheter or tube is pushed inward, inverting this portion of the gut. Interposition of omentum and the use of skin sutures to hold the cath-

ter firmly is indicated, when possible, to afford close approximation to the parietal peritoneum, to give protection against leakage.

*Postoperative care* should be directed toward maintenance of the fluid balance by giving **sodium chloride** and **glucose solutions** intravenously and subcutaneously. To relieve upper-abdominal distention and intestinal stasis, the use of **suction siphonage** (Wangensteen) with the **per-nasal duodenal tube** is an outstanding aid.

In regard to the *differential diagnosis of inflammatory conditions of the liver* with pus collections, in a single abscess of the liver, the history of the patient is important, on account of its association with amebic dysentery. Multiple abscesses of the liver usually follow previous infection in the abdomen, such as appendicitis and gall-bladder infections which find their way through the portal circulation to the liver. The treatment of *simple abscess of the liver* consists of **simple drainage** after proper walling off of the peritoneal cavity. In *multiple abscesses*, operation is of no avail because the condition of pyemia is usually present.

The use of the aspirating needle is to be deplored in differentiating gumma of the liver from metastatic carcinoma and echinococcic cysts. It is especially dangerous where fluid is present, on account of causing peritoneal contamination. Surgical intervention is a much better plan. In echinococcic cysts, **marsupialization of the cyst** is considered good treatment.

In *acute cholecystitis*, the final analysis dictates that **cholecystectomy** is the operation of choice, except when jaundice is present. In this latter group, **cholecystostomy** should always be performed on account of the greater danger of hemorrhage ensuing as a result of stripping off the gall-bladder in a jaun-



diced patient. In acute cholecystitis with empyema, the surgeon should hospitalize the patient and wait until all acute inflammatory symptoms have subsided, when there is no danger of doing a cholecystectomy.

In *chronic cholecystitis*, it is believed that too many cholecystectomies are being performed. Surrounding structures should be investigated, particularly the pancreas. When the pancreas has hardened as result of inflammation, a **cholecystogastrostomy** or **duodenostomy** should be performed.

In operations for *cholelithiasis*, it is always important, especially when there has been a history of jaundice, to examine the common bile duct. This surgery is much more difficult and more hazardous than surgery of the gall-bladder alone, with a higher mortality. The presence of stones in the common duct varies greatly. Lahey's statistics show that 20 to 30 per cent. of cases operated upon have common duct stones.

There is great danger of surgery in the presence of jaundice, hemorrhage being the greatest danger. Other dangers include cholangitis and cholemia. Degeneration of the heart muscle and other organs result and, at times, acute mania and melancholia have accompanied the condition.

#### ABDOMINAL APOPLEXY.—

A case of fatal nontraumatic, nonmalignant hemorrhage into the peritoneal cavity of a male is reported by M. T. Moorehead and J. S. McLester (J. A. M. A. 106:373 (Feb. 1) 1936). The patient had vascular hypertension and was in bed for 27 days, when he suddenly developed signs and symptoms pointing toward internal abdominal hemorrhage. At autopsy, it was found that the gastric artery, which showed a marked degree of atherosclerosis, had ruptured at the juncture of the right

and left branches on the midportion of the lesser curvature. Another case of fatal intraperitoneal hemorrhage was observed in a white man, aged 50. The patient was being treated for pulmonary emphysema and myocarditis and was in bed, when, on the forty-sixth day he died with evidence of recent internal hemorrhage. At autopsy, approximately 3000 c.c. of blood and recently formed blood clots were found in the abdominal cavity. The tunics of the superior mesenteric artery were split for a distance of several centimeters by a dissecting aneurismal hemorrhage. The authors conclude that more people live to an old age now than formerly, and, therefore, more people have time to develop arteriosclerosis. Other factors, such as faulty diet and a faster tempo of life may also operate in the same direction.

**ABDOMINAL INJURIES.**—An interesting review of the sequelæ of *penetrating wounds* of the abdomen, based on a critical study of the reports on 606 persons wounded in the war of 1914 to 1918, is made by duBourguet (Rev. de chir. 74:175 (Mar.) 1936). The lesions reviewed by the author were of the following types: lesions of the abdominal wall, .287; peritoneal lesions, 103; canalicular lesions (lesions of the intestines, biliary passages, etc.), 25; fistulas, 82; lesions of solid organs (retained foreign bodies), 97; and late abscesses, 8. There were, of course, many overlapping lesions, such as a serious loss of substance of the abdominal wall associated with intraabdominal lesions of considerable extent. However, each case is included in only 1 group.

The 287 *lesions of the abdominal wall* included 144 abdominal hernias, 28 diaphragmatic hernias, 113 adherent scars, 4 other lesions, and 2 aneurisms. The abdominal hernias included 98 postoperative hernias, of which 64 were small,

19 of medium size, and 15 extensive; 27 large hernias with loss of substance; and 9 paralytic hernias. In the cases of small postoperative hernias, the incidence of invalidism was about 10 per cent.; in those of hernias of medium size it ranged from 10 to 65 per cent. and averaged about 30 per cent.; and in those of large hernias it ranged from 60 to 65 per cent. In the 27 cases of hernia with loss of substance it ranged from 40 to 70 per cent., and in the 19 cases of paralytic hernia, from 10 to 40 per cent. The symptoms were due largely to displacement of organs and adhesions to the hernia or scar.

*Small hernias* can be controlled by the wearing of a truss or belt, but for *large hernias* **operation** is desirable. The author describes briefly various operative measures for the cure of hernia, *i. e.*, simple closure, overlapping procedures, and plastic repair. He states, that in general, the results of operation are good, but many patients refuse operation, preferring a truss and a pension. The procedure indicated for *paralytic hernias* consists in **resecting the atrophied muscle zone and suturing the edges**.

In cases of *diaphragmatic hernia* operation is necessary, as a rule, as traumatic hernia of this type is usually serious. Of the 28 cases reviewed, operation was performed in 23, with death in 5, and cure in 18. Of the 5 patients not operated upon, 2 were dead and 3 were living at the time of the report.

Of the 113 patients with *adherent scars*, 37 had only subjective symptoms. In general, the incidence of invalidism in this group was rather low. Surgical treatment is not often indicated for adherent scars. It should consist of **excision of the scar and resuture of the wall in layers**.

In 103 cases of *peritoneal lesions complications* were divided into 2 groups: (1) 68 of deep adhesions, and (2) 35 of perivisceritis. In the first group the common symptom was pain often associated with difficulty in passage of the intestinal contents without actual obstruction. In the second group the complications were gastric distention, slow emptying of the stomach and duodenum, visible and audible peristalsis, and vague and often rhythmic pains. The incidence of invalidism in this group ranged from 10 to 45 per cent., but averaged 25 per cent. As a rule, surgical treatment is indicated. It should consist of **freeing of the adhesions or short-circuiting**.

Of the 25 cases of *canalicular lesions*, intestinal stenosis occurred in 24 and stenosis of the biliary tract in 1 case. Because of the frequency of multiple adhesions, direct approach to the lesion is rarely possible and **short-circuiting** is necessary. In the case of *biliary obstruction*, **cholecystogastrostomy** was done.

Of the 86 *fistulas*, 5 were biliary; 37, urinary; and 44, fecal. In cases of *biliary fistula* there is a tendency toward **spontaneous cure**. If spontaneous cure does not occur, operative intervention—either **plastic restoration of the ducts** or **short-circuiting**—is necessary. Of the 37 urinary fistulas, 31 were vesical and 6 vesicorectal. The *vesical fistulas* were usually of the intermittent type with periods of drainage. Operation was seldom indicated for such fistulas except for the removal of foreign bodies. For the closure of *vesicorectal fistulas*, **multiple operations** are usually necessary. Of the 44 *fecal fistulas*, about half **healed spontaneously**. The rest required surgical closure.

Of the 97 lesions involving solid structures and due largely to *retained foreign bodies*, 3 involved the abdominal wall;

2, a kidney; 1, the spleen; 1, the peritoneum; 5, the omentum; and 60, the liver. **Operative removal** of the foreign body is often indicated for such lesions.

In conclusion, du Bourguet calls attention to the fact that penetrating wounds of the abdominal wall are generally more persistent and important than intraabdominal lesions. The former tend to become worse, while the latter tend to become cured spontaneously. Most of the late sequelæ are fairly amenable to surgical treatment.

H. A. Oberhelman and E. R. LeCount (Arch. Surg. 32:373 (Mar.) 1936) outline the results obtained in peace time in 343 cases of *bullet wounds of the abdomen* treated at the Cook County Hospital, Chicago, during the period from 1911 to 1924, and trace the development of the treatment of such wounds from 1925 up to the present time. From the literature they collected 494 cases in which laparotomy was performed. Of these, 789 (52.6 per cent.) terminated fatally.

In the Cook County Hospital series of cases the wounds were such as are usually produced by homicidal, suicidal, and accidental shootings in large cities. None of them was due to the kind of machine guns now used by gangsters. Only 1 was produced by a shotgun. Of the 222 patients who died, laparotomy was performed on 169, and 205 came to autopsy. Of the 37 patients who died without operation, 33 were either moribund or in poor condition when they entered the hospital.

The largest group of cases with wounds involving a single abdominal organ were 41 cases of *injuries of the small intestine*. Of the 301 cases in which laparotomy was performed, injury of 2 or more viscera was found in 182. The mortality in the latter

group was 80.7 per cent. Forty-three patients had wounds of both the *abdomen and the thorax*. Of the 31 of this group who were operated upon, 24 died; whereas of the 12 who were not operated upon, all died. Of the 169 patients coming to autopsy after laparotomy, *overlooked wounds* were found in 94. As undoubtedly there were overlooked wounds in some of the cases in which recovery resulted, the incidence of overlooked wounds in the entire series is not known.

The authors' study indicates that when death occurs within 24 hours after a bullet injury, it is due to hemorrhage and shock; whereas when it occurs later, it is usually due to generalized peritonitis.

The case report of *traumatic rupture of the upper jejunum* to demonstrate the successful results of early operation with primary closure of the abdomen in such cases is cited by A. La Ragione (Arch. ital. di chir. 43:115, 1936). The patient, a man 33 years old, was kicked by a horse, the blow falling obliquely from the left on the umbilical region. At operation, 5 hours after the injury, a small perforation was found on the free border of the intestine from 20 to 30 cm. below the duodenojejunal flexure. There was no lesion of the mesentery. The intestine was closed with Lembert sutures, the peritoneum cleansed, and the abdominal wall closed. Recovery was uneventful. The mechanism of the trauma appears to have been a crushing of the intestine against the spine.

The author discusses the various mechanisms involved in rupture of the intestines; the differential diagnosis of intestinal perforation, with particular reference to the behavior of the pulse; the necessity for operation as soon as the shock has passed off; and the question of primary closure of the abdomen.

**HEPATIC TRAUMA.**—E. G. Krieg (Arch. Surg. 32:907 (May) 1936) reviews 60 cases of hepatic trauma admitted to the City of Detroit Receiving Hospital during the period from 1927 to 1934 inclusive. In 68 per cent. the injury was due to a bullet; in 17 per cent., to an automobile or street-car accident or a fall; and in 15 per cent., to stabbing. Signs of shock were present or reappeared after treatment and continued until death in 73 per cent. In the 24 cases in which complete blood counts were made, there was laboratory evidence of anemia at the time of the patient's admission to the hospital. In 55 cases operation was performed promptly after adequate response to treatment for shock and hemorrhage. Five patients were treated medically. Of the latter, 2 died within 3 hours, and 3 who were children in an extreme state of shock, showed no improvement until after the third day.

The hepatic wounds were of four types: (1) clean incisions produced by stabbing; (2) clean punctures due to bullets; (3) macerating punctures due to bullets; and (4) rough fractures produced by contusion. In 41 cases the liver was the only organ involved, whereas in 21, in all of which except one the wound was caused by a bullet, some other organ was also injured, usually the spleen. Abdominal hemorrhage of variable degree was always present.

The mortality in the entire series was 61.6 per cent. Hemorrhage and shock caused death in 73 per cent. of the cases in which they occurred. Death resulted within 3 days.

**Symptomatology.**—The chief clinical features are pointed out by W. M. Shedden and F. Johnston (New England J. Med. 213:960 (Nov. 14) 1935) as follows: (1) Pain in the right upper quadrant, though the pain may be generalized throughout the abdomen or

not present at all. McKnight states that if the convex portion of the right lobe is injured, pain is referred to the right scapular region, while if the concave portion is involved, the discomfort is referred to the waistline anteriorly. Bloch reports a case of ruptured liver in which the maximum tenderness was in the left lower quadrant. (2) Board-like hardness and exquisite tenderness over the involved area is a rule. (3) Increase in liver dullness, upward or downward. (4) Shock, due to the single impact or to the flooding of the peritoneal cavity with blood or bile, though there have been many reports of cases of ruptured liver with little or no clinical signs of this phenomenon. Death ensued 5 hours after the operation. The degree of immediate shock, therefore, does not represent the injury often enough to be a guide in cases where no shock is observed. Free exposure and hemostasis at the earliest possible moment is advised. (5) A sharp rise in the leukocyte count and a slower fall in the erythrocyte count and hemoglobin. The leukocytic reaction presents a characteristic curve reaching a height of 150 to 300 per cent. within the first 10 hours. (6) Jaundice, though this phenomenon seldom appears before the third or fourth day, if at all. McKnight advances the theory that the jaundice may be due to the shattering of Glisson's capsule. He reasons that as a result of this laceration, the secretory pressure of the liver is decreased and the bile dammed back and forced into the lymphatic channels. It may, of course, also be due to hepatic sepsis. Andersson reports the case of a laborer who developed jaundice 2 weeks after an abdominal injury. Exploratory laparotomy 9 days later revealed a liver abscess. The hepatic capsule was intact. (7) It must be remembered that liver rupture is sometimes accompanied by a slow pulse.

**Differential Diagnosis.**—1. Simple shock. Hourly blood counts will aid in deciding upon or rejecting this diagnosis.

2. Simple traumatism to abdominal wall. Blood examination will also help here. White has also employed diagnostic aspiration of the peritoneal cavity with a large needle.

3. Splenic rupture. Though the pain and tenderness are usually in the left upper quadrant of the abdomen, the symptoms here may be identical with hepatic rupture and the lack of localizing signs, of course, does not rule out trauma to the liver.

**Prognosis.**—This seems to depend on (a) the amount and rate of hemorrhage; (b) the escape of bile into the peritoneal cavity, which may be a contributory cause of paralytic ileus; (c) the amount of destruction of liver tissue; (d) the presence or absence of injury to structures other than the liver.

**Treatment.**—When possible, **immediate operation** is essential. The importance of early recognition and prompt institution of surgical measures can best be emphasized by Thole's statistics. He demonstrated from a study of 260 cases of ruptured liver that if operation takes place within 6 hours, the mortality is 40 per cent.; between 7 and 12 hours it is 50 per cent.; while between 13 and 24 hours it is 67 per cent. After 24 hours the mortality rapidly mounts to 86 per cent., though cases have been operated on with recovery 2 to 30 days after liver rupture.

If blood cannot be obtained from other sources, **autotransfusion of blood** may be employed. However, the presence of extravasated bile and the possibility of the presence of the contents of hollow viscera should make this a procedure to be done only after careful abdominal exploration.

It may be found on opening the abdomen that the hemorrhage has ceased

and that a careful **removal of the blood** and an **abdominal closure** are all that is necessary.

If the bleeding is not severe, a **gauze pack** may be sufficient to check the *hemorrhage*. The **hepatoduodenal ligament** may be **compressed** while the packing is inserted. Graham states that this ligament may safely be compressed for a half-hour. It is probably well to remove the pack after 48 hours under general anesthesia. Drainage introduces infection and occasionally causes a secondary hemorrhage. Robin describes a case in which the pack was left in for 2 weeks. A liver abscess resulted. The third week the patient had a series of secondary hemorrhages.

If the bleeding is checked when the pack is removed, a **piece of rubber** may then **be inserted to the level of the peritoneum**, in order to take care of a possible later leakage of bile.

If the pack does not check the hemorrhage, **suture of the liver** should be attempted, employing if possible a large blunt needle.

If a large amount of liver tissue had been damaged, it is probably well to administer **glucose** freely. It has been clearly demonstrated that hepatectomized animals die because of a glucose deficiency.

## **ABDOMINAL TRAGEDIES.**—

**Differential Diagnosis.**—M. Lick (Pennsylvania M. J. 39:421 (Mar.) 1936) states that the sufferer is frequently first seen under conditions unsatisfactory to the examiner. The light is poor, the bed is low, the room is small and is crowded with tearful, anxious relatives, among whom there is always one, with stern unfriendliness, who does not believe in hospitals or operations. All this often creates an atmosphere uncondusive to calm, logical thinking and clear judgment.

Amid these conditions or even among those advantageous ones of the hospital, the surgeon is confronted with a problem of diagnosis. It is usually fascinating, but all too often blurred and confusing. Is the condition surgical, or are the abdominal signs and symptoms but a red herring drawn across the trail to confuse the examiner and conceal the true condition?

Observation of the patient may speak volumes. The impression of a *peritoneal disease* may be gotten at a single glance. The knees may be drawn up, the tongue coated, and the basin close by for vomitus; the facie may present an expression of anxiety, suffering, and a sense of impending disaster. It is difficult to describe this expression, but it can be recognized by the experienced. It is never absent in acute peritoneal conditions. If this is not seen, the physician should be exceedingly wary in diagnosing an acute condition within the abdomen, even though other signs seem conclusive. At times, Lick has offended his confrères by refusing to open an abdomen which was rigid and painful because the patient looked too comfortable. He was out of balance with the abdominal signs. These cases almost invariably turn out to involve referred symptoms from the chest or diaphragm. Physicians are all familiar with the flushed cheek, the slight increase of respiration, the slight cough heard occasionally during the conversation, which should immediately excite the suspicion of a *chest lesion* regardless of the abdominal signs.

Perhaps all these things and more are caught in one glance before any story of the disease is elicited. The story is so important. Murphy said that if it were told correctly, the diagnosis would stand out as though written in large letters. The fault often lies with the physician who is hurried or impatient

with a loquacious patient or his relatives. It takes skillful cross-examination at times to get at the truth, to separate the inconsequential from that which is relevant. It can and should be done. The *ruptured ulcer* should give a history of previous digestive disorders quite different from that of the *acute gall-bladder* with its usual story of flatulent indigestion. In cases in which the picture is either that of subacute perforation or acute cholecystic disease, the ratio of ulcer is 3 to 1 for men, whereas that of gall-bladder disease is just the reverse, being 3 to 1 for women.

*Carcinoma of the large bowel with obstruction or perforation* would be suspected in an elderly patient with an acute abdominal crisis, whose history related blood in the stools and a disturbance of bowel habit. A history of functional disturbance of the pelvic organs must not be dismissed as irrelevant merely because the abdominal signs do not conform to the textbook pattern. Physicians miss more things from not thinking than from not knowing. It is almost a truism that, if a diagnosis does not ring true, something unthought of will be found at operation.

*Pain* is probably the most constant and outstanding symptom of the acute abdomen. Pain is a clarion cry. It is nature's flashing signal that harm or injury is being done. It sends the mother, white-faced, to call the doctor when she hears the shrill cry of her sick child. A proper interpretation of pain alone may make a diagnosis certain.

It should be emphasized strongly that continued abdominal pain usually indicates a surgical condition. It must be asserted just as earnestly, however, that not all abdominal pain indicates abdominal disease. Those overflow pain impulses from the chest and diaphragm are not so severe. They disappear or are modified in a few hours. The cor-

responding signs and symptoms of acute abdominal disease are lacking or are not parallel. Tenderness is not commensurate with rigidity. The pulse rate is too slow. It does not have the quick, discourteous slap. The facies are more comfortable. This discrepancy and contradiction should be a warning, and observation should be practiced for a few hours. This can be carried too far in children. Late cases of *appendicitis* with local or spreading *peritonitis* usually show moisture in the lungs or other signs which blue the picture to one who is called to see the case late. The trajectory of the pain in *coronary disease* and *angina pectoris* is frequently to the gall-bladder. Nausea, vomiting, and local spasm of the recti muscles sometimes recur. The old, old story of "acute indigestion!" The cue here, of course, is the accompanying substernal pain, the dyspnea, the tone of the heart, the history of circulatory derangements, the absence of digestive disturbances in the foreground.

Everyone is familiar with those overflow pain impulses from the *ureter* or *kidney* which may simulate the most violent abdominal disease. The condition is well illustrated by a patient who was brought to the hospital in the night with poignant, colicky pain, nausea, vomiting, and distention. To make the diagnosis plain, there was an appendix scar. Obstruction, of course! This man was fortunate in having a painstaking, thorough, meticulous analytic surgeon. Why should this pain be felt, even though slightly, in the testicle or over the hip? Abdominal pain is never referred here. A urinalysis disclosed a few red blood cells; cystoscopy, a *horseshoe-kidney* and a *blocked right ureter*. The point to be emphasized is that the cues are usually present. They are the red entries in the ledger. They may be upstage in the shadows. They are missed from not thinking, or the physician fails

to be impressed because they seem to be so trivial compared with other signs. It cannot be emphasized too strongly that a single urologic cue should be given the greatest consideration even though the abdominal picture stands out in strong light. Recourse to the cystoscope, the microscope, and x-ray is indicated and causes little delay.

Little need be said about the *pain of ruptured ulcer*. This is one disease, with its sudden agonizing, brutal attack, its rigid muscles, and its capacity to absorb morphine without relenting, that runs true to the textbook picture. Several facts have impressed the author. There are silent ulcers, the first sign of which is that of rupture. The history fails in these cases. Shock is not always marked, and the pulse is not always as rapid as would be supposed. The facies are never forgotten. The anxiety, the suffering, the sense of disaster and dissolution are all mirrored. When this picture is present, the diagnosis cannot be denied even though the history for ulcer is absent.

However, if this picture is so modified that all symptoms and signs are softened, if the knees are not drawn up, if the muscles are not hard enough, if the patient looks more comfortable than he should, *i. e.*, if his general appearance is disproportionate to the abdominal pain, caution is advised.

In acute abdominal disease with general pain and tenderness there is always one spot more tender than the rest, and it hurts when the patient moves in bed. This observation has been of inestimable value and bears repetition. The ruptured ulcer is exquisitely tender over its area. It is known that this is true of *appendicitis*, because the only constant sign is that of focal tenderness. There may be spreading or general peritonitis present, but the appendix region is still the most tender. It is

deplorable that more attention is not given in the teaching of medical students to this point of focal tenderness in the diagnosis of appendicitis. Most interns look for rigidity, leukocytosis, fever, and pain in the epigastrium, which moves down to the right side. Violent forms of the disease exist with some of the signs absent or so modified that only the experienced can interpret them correctly. But focal tenderness of the diseased organ is always present.

The *pain of intestinal obstruction* is striking. It is colicky and usually felt first in the upper abdomen. It comes and goes. The patient looks sick. There is nausea and later vomiting. Peristalsis is usually heard. And yet with this characteristic and usually unvarying picture, it is often missed. If this is doubted, the late and hopeless cases operated upon in the hospitals should be recalled to mind. Why should this be so? Some still forget that gas or feces will be passed from below the obstruction. Some still fail to look at the hernial orifices, or for abdominal scars. Some still wait for fecal vomiting and terrifying distention. It is a disgrace for any of the profession to wait for these premortal changes. Operation at this time is hopeless and only gives occasion for the usual headlines in the next day's paper, "Patient Dies of Operation." It should read, "Patient Dies of Delay." There is no disease that has a narrower threshold of safety. There is no disease that needs more prompt action. It takes courage in the postoperative cases to tell the sick and discouraged patient and his anxious and often unfriendly and doubtful relatives that another operation is necessary. Delay in the presence of these faithful symptoms only makes matters worse, whereas prompt and courageous action will save most of these unfortunate cases.

These foregoing principles are elementary but certainly fundamental. It should be remembered that disease of any system or organ results in a disturbance of function of that organ. The signs and symptoms are always present to some degree. Confusion and mistakes occur by reason of the physician's inattention and prejudices. It is helpful to remember that after age 40 practically no new abdominal diseases exist except neoplasm and inflammations, all others being complications of preëxisting conditions. It is pertinent to remember, as DaCosta said, that an absent sign should be given grave consideration. Finally, it is invaluable to remember the tendencies, the conventionalism, if you please, the relation of acute disease to age and sex.

**POSTOPERATIVE COMPLICATIONS.**—R. L. Rhodes (Ann. Surg. 103:804 (May) 1936) reports 2 unusual cases of *gas-bacillus infection*. In the first, that of a colored man 35 years old, operation was performed for strangulated hernia. At the time of the operation the odor characteristic of gas-bacillus infection was not recognized. The patient died soon after the operation. At autopsy, the peritoneal cavity was found to contain foul-smelling gas and bloody fluid. The small intestine was markedly distended with gas.

The second case was apparently one of *gas-bacillus infection* of the intestinal tract. The symptoms were those of intestinal obstruction with apparent prostration and enormous abdominal distention. The patient survived only a few hours. Cultures of the peritoneal fluid made at autopsy yielded the *bacillus welchii*.

In trying to explain the sequence of events in the second case, the author says that trauma and interference with the blood supply of the muscular tissue



of the wall of the bowel may have been responsible for the entry of the Welch bacilli. This theory is supported by the well-known rapidity of growth of the bacteria in traumatized muscle. In neither case was a gross perforation of the bowel found at autopsy.

A group of 6 cases of *chronic, ulcerative, burrowing, nongangrenous lesions of the abdominal wall* apparently due to a microaerophilic hemolytic streptococcus is presented by F. L. Meleney (*Ibid.* 101:997 (Apr.) 1935). The lesions in the last 3 cases responded strikingly to local treatment with zinc peroxide.

The characteristic features of the infection begin gradually. What appears to be an ordinary drainage tract from a deep or subcutaneous abscess fails to follow the usual course of healing. The skin margins become undermined and the edges roll in. There is no gangrene, but a gradual liquefaction of the skin margins, with the production of a progressive ulcer. Daughter ulcers form either by liquefaction of the skin from beneath or by the introduction of the organism from without. Sinuses form as the infection burrows down between the muscles. In lesions of the lower part of the abdomen the undermining frequently spreads down toward the groin or the pubic region, extending into the vulva or scrotum or beneath the crease of the groin into the thigh. In these regions it may extend inward, dissecting beneath the muscles and forming deep sinuses into the pelvis. Occasionally, one margin shows a spontaneous tendency to heal. However, instead of progressing steadily, the margin of the new epithelium may suddenly become clear-cut and remain stationary for a long period of time or rapidly melt away.

In most cases the lesion is only moderately painful, but in some the pain may be excruciating. There is usually a daily rise in the temperature to be-

tween 101 and 103° F. (38.3° and 39.4° C.). This fluctuates markedly from week to week. During the periods of fever the patient is usually greatly prostrated. In the course of time the lack of response to treatment brings great discouragement and gradually breaks down the patient's morale, sometimes to such a degree that the patient expresses a desire to commit suicide. After months or years of suppuration, the lesion occasionally heals spontaneously, but as a rule, the ulcer spreads and the sinuses burrow deeply and cause death from the erosion of a large vessel or the gradual development of amyloid degeneration of the liver, spleen, and kidneys.

The only effective *treatment* yet found is the daily application of **zinc peroxide**. This has been found to kill the causative organism also *in vitro*. It must be thoroughly applied to every part of the infected surface. Under such treatment the sinuses will close, the undermined flaps will heal, and new skin will grow in from the margins. The defect may then be closed with skin grafts.

The essential organism in the infection is a hemolytic streptococcus which prefers an anaerobic environment. Its immediate source is probably the intestinal tract or the vagina. In 4 of the 6 cases reported it could be obtained only by anaerobic cultivation. In 2 of these it was present in pure culture. In 2 of the long standing cases it was found with aerobic cultivation. However, even when it was obtained aerobically it was found to grow very much better anaerobically. After artificial cultivation on meat medium, it gradually takes on aerobic properties and after a few generations will grow on the aerobic plate. It shows the usual cultural characteristics of beta hemolytic streptococci. It may have been originally an ordinary aerobe which adapted itself to the anaerobic environment of the intestinal tract.

According to J. H. Powers (J. Thoracic Surg. 5:306 (Feb.) 1936), abdominal operations are followed by a postoperative decrease in the vital capacity. *Postoperative pulmonary complications* are related to lowering of the vital capacity. An incision in the upper part of the abdomen causes a markedly greater lowering of the vital capacity than an incision in the lower part of the abdomen. Operations on the extremities or perineum do not seem to affect the vital capacity.

**Pulmonary hyperventilation** immediately after anesthesia and for the first 3 days after operation was suggested by Henderson and Haggard as a *prophylactic measure against pneumonia*. This method has been investigated by many workers, some of whom report favorable results whereas others state that they noted no marked improvement.

The author reports on a small series of cases in which he studied the effect of hyperventilation on the vital capacity. The vital capacity was determined daily, before and after operation, by means of a Collins spirometer. All observations were made at least 2 hours after meals with the patient in the semi-sitting position. The readings represented the best expiratory and inspiratory effort for each day. Only cases without drained wounds were studied.

The 5 cases of operation on the upper part of the abdomen which were treated by hyperventilation showed an increase of from 16 to 23 per cent. in the vital capacity as compared with the untreated cases, and the cases of operation on the lower part of the abdomen an increase of from 23 to 26 per cent. as compared with the controls. Although the number of cases was small, these findings indicate that hyperventilation keeps the vital capacity at a level higher than that in cases in which it is not used.

Changes in the usual course level of the vital capacity are indicative of a post operative complication. Lowering of the vital capacity may occur much earlier than it is recognized clinically. In a case of hematoma in an abdominal wound, for example, the vital capacity may occur much earlier than it is recognized clinically. Abdominal binders, adhesive strapping, and surgical abdominal dressings do not influence the vital capacity to any marked extent.

The procedures used in *getting patients out of bed early after abdominal surgery* are discussed by A. Charbonnier (Rev. méd. de la Suisse Rom. 55:402 (June 25) 1935). The author calls attention to the fact that the incidence of phlebitis and embolism is very low when the described method is used. This is probably explained by the prevention of venous stasis.

The patient must be hospitalized a full day before the operation. In the author's cases **saline solution** and **glucose** are given to improve nutrition or relieve dehydration. If possible, **exercises** are given to **increase pulmonary ventilation and improve the peripheral circulation**. Patients subject to *respiratory infection* are treated with **vaccines**.

Careful attention is paid to asepsis, hemostasis, and closure of the wound. After the operation, **saline solution and water** are given in large quantities. To combat shock, the **foot of the bed is raised** on wooden blocks. The **wound is dressed tightly** and an **abdominal binder** then applied.

On the first day after the operation the attendant aids the patient in making pedalling movements with the legs. This exercise is preceded or followed by an alcohol rub. The patient is encouraged also to raise himself by grasping a trapeze suspended above the bed and to take deep breathing exercises.

On the second postoperative day the movements are increased and intestinal peristalsis is stimulated by rectal lavage.

On the third day the exercises include hanging the legs over the edge of the bed and semisolid food is given.

At the visit of the surgeon on the fourth day, if the condition of the abdomen, the pulse, and the temperature are satisfactory, the patient is carried to his chair and allowed to sit with his feet resting on the floor for from one-half to one hour.

On the fifth day he is allowed to walk to the chair and to sit in it for 2 or 3 hours if his condition is satisfactory.

On the sixth day he is permitted to walk about the room.

On the ninth day walking up and down stairs is begun.

Between the twelfth and fifteenth days the patient is permitted to return to his home if he is able to be out of bed, most of the time walking about or engaged in light tasks.

In cases in which there is extensive infection or drainage from the *abdomen* or *vagina* the patient is kept in bed for from 15 to 20 days. In cases of operation for *hernia* he is kept in bed until the twelfth day because of the friability of the tissues and the ease with which hematomas are formed.

In cases of cardiac, renal, or hepatic deficiency, those of prolonged postoperative shock, and those with severe hemorrhage the described routine is contraindicated.

Charbonnier believes that **early ambulant treatment** is a step forward in surgical treatment as it will be found beneficial in at least 50 per cent. of cases in which an abdominal operation is performed. For successful results it must be employed judiciously and carried out carefully.

### APPENDICITIS.—*Etiology.*—

The present status of the problem of appendicitis is outlined by A. D. Bevan (S. Clin. North America 16:63 (Feb.) 1936). The author briefly traces the history of knowledge of appendicitis from the time of Reginal Fitz in 1886 to the present day.

He ascribes the condition to a local inflammation beginning in the mucosa of the appendix at an atrium of infection caused by injury from fermentative products produced in the intestinal tract or by a foreign body, and extending through the other coats of the appendix to reach the peritoneum. He calls attention to the clinical picture as the basic factor in the diagnosis, placing minor emphasis on laboratory findings. He states that if medication is given at all, early in the disease, he recommends the use of minute doses of *atropine* as an aid in differentiating "spasms" from appendicitis.

**Operation** within the first 48 hours of the attack is advised. On the third, fourth, and fifth day it should be performed immediately, unless the symptoms are subsiding. When the symptoms are subsiding, watchful waiting is indicated. If a palpable inflammatory mass is evidenced about the appendix which daily becomes less tender, expectant treatment is advisable. If no immediate indication arises for surgery, delay of appendectomy for from 6 to 8 weeks is indicated.

### *Symptomatology and Diagnosis.*—

In a review of 2921 cases of appendicitis by M. R. Reid, D. H. Poer and P. Merrell (J. A. M. A. 106:665 (Feb. 29) 1936) admitted to the Cincinnati General Hospital in the period from January 1, 1915, to January 1, 1934, it was found that 2035 were diagnosed as acute appendicitis.

Forty-one per cent. of the patients had had previous attacks, and in the cases of 42.5 per cent. the appendix

was ruptured at the time of the patient's admission to the hospital. The average duration of the attack before admission was 3.8 days. Abdominal pain, the most prominent symptom, occurred in 94 per cent. of the cases. Pain on pressure over the appendix was present in almost all, and seemed to be the most important single finding. The next most important symptoms were nausea and vomiting, which occurred, respectively, in 70 and 80 per cent of the cases. As tenderness, induration, and a mass were found on rectal or pelvic examination in 44 per cent. of the cases, the authors believe that these procedures are of great value. Thirty-six per cent. of the patients had taken purgatives prior to their admission.

In 576 (66 per cent.) of the 865 acute cases with perforation, a localized abscess formation was found. In 33 per cent. of the cases with perforation there was peritonitis of varying degree. In the majority it was advanced and widespread.

To determine why benefit may result from the removal of appendices showing little evidence of inflammation, O. I. Cutler (Arch. Surg. 31:729 (Nov.) 1935) compared the complaints of a group of patients with the findings at operation and the condition of the appendices removed. The appendices studied consisted of 344 removed in the past few years in one hospital. This series represented cases of frankly acute inflammation of the appendix, a number of cases in which removal of the appendix was done as a routine procedure at operation on some other organ, and cases of so-called chronic appendicitis. The observations made in the different groups of cases are recorded separately and briefly correlated. The appendices removed at the time of operation on some other organ were used as a control group.

Among the 344 cases studied, there were 103 in which the appendix appeared to be the site of trouble but presented only slight or no evidence of an active inflammation. The most constant and impressive evidences of abnormality in the 103 appendices were indications of a functional disturbance rather than of inflammation. The appearance of the appendices and a few clinical observations in the chronic group of cases are discussed. Statistics concerning the 77 cases of frankly acute inflammation are briefly given. There were 8 cases of healing acute appendicitis in this series and 34 of early or mild acute appendicitis.

Cutler believes that the failure of the appendix to empty properly is a common cause of repeated attacks of *pain in the right lower quadrant of the abdomen*. He states that such pain is frequently associated with reflex nausea and vomiting. In many cases the cause of obstruction is spasm of the muscularis of the ampulla of the appendix. Elevation of the temperature and leukocyte count appear not to occur unless acute inflammation is present. Cutler believes that until some better method of relieving obstruction is found, removal of the obstructed appendix is warranted. Appendiceal colic due to obstruction may be most distressing. The study of the control series of cases indicated that some patients may have appendiceal obstruction and complain of it relatively little. Many attacks of acute appendicitis are very mild. Repeated mild attacks may cause thickening of the submucosa and narrowing of the lumen, with resulting appendiceal obstruction and obliteration of the lumen of the appendix. Frequently, attacks of acute appendicitis are very mild and unrecognized. A study of the blood count, particularly the Schilling count, is of definite aid in determining the severity of the condition.

Since it is not possible to predict accurately the course of events in the appendix, early operation is urged.

M. Titone (Arch. ital. di chir. 40:1 1935) reports a study of *gastric function* made both before and at least 20 days after appendectomy in 20 cases of appendicitis. From his findings he concludes that when there is no inflammation around the stomach or duodenum, the gastric disturbances in appendicitis are related to a disturbance of the vago-sympathetic system caused and maintained by a usually subacute or chronic inflammation involving not only the appendix, but also some other abdominal organ, as a rule an organ in the right side of the abdomen. This disturbance, which is often favored by a constitutional condition (vagotonia), produces a gastric syndrome based usually on hyperchlorhydria and hypermotility, but sometimes, though infrequently, on hypochlorhydria and hypomotility.

When the symptoms are caused by hyperchlorhydria and are maintained by inflammation of the appendix, simple *appendectomy* gives good results if it is performed early.

**Complications.**—*Peritonitic ileus* complicating acute appendicitis is not a common condition. It becomes extremely serious if it is not recognized early and dealt with properly. In the opinion of W. S. Handley (Proc. Roy. Soc. Med. 29:163 (Dec.) 1935), jejunostomy, which at present seems to be the operation of general choice, is not the solution of the problem. Medical measures must not be continued too long. Continuous **gastric aspiration** by means of the **indwelling catheter** is often of great value.

*Peritonitis* is rarely general even at the time of death. It begins most frequently in the pelvis and may gradually spread upward to reach the hypogastric region. In the flood-like invasion of the peri-

toneal cavity from below upward, the stomach, jejunum, transverse colon, liver, and diaphragm remain uninflamed and unparalyzed until the patient is moribund. This fact is the key to successful treatment.

The author recognizes 3 stages of unlimited peritonitis: (1) pelvic peritonitis, (2) hypogastric peritonitis, and (3) the hopeless clinical picture of the textbook type. Ileus may remain absent during the pelvic stage of peritonitis and may supervene only in the hypogastric stage. When the hypogastrium becomes distended, the time for action is short. The author **anastomoses a distended coil of jejunum to the transverse colon** and opens the cecum by **cecos-tomy**. Reflux occurs from the transverse colon and ascending colon to the cecostomy. Within 24 hours after this operative procedure, free fecal discharge occurs and the abdomen becomes soft and flat. The author has performed this operation in 5 cases, with recovery in four. In the fifth, the patient recovered from the peritonitis, but died one month later of pyemia. In all of these cases there was an intense and apparently hopeless streptococcal peritonitis with obstruction which failed to respond to medical treatment.

**Pathology.**—Observations on the pathology of appendicitis by A. J. Trinca (Australian and New Zealand J. Surg. 5:258 (Jan.) 1936) lead him to believe that the primary causative factor in appendicitis is not bacterial invasion of the mucosa of the appendix.

In a study of the *blood supply* of the appendix, 5 main variations are noted:

1. An appendiceal artery supplying the appendix only.
2. A cecal artery supplying the proximal portion of the appendix.
3. The proximal portion of the appendiceal artery supplying a portion of the cecum.

4. An accessory appendiceal artery supplying the proximal portion of the appendix.

5. An appendix bound to the wall of the cecum supplied by small cecal arteries and with only a rudimentary appendiceal artery.

Trinca notes that the appendiceal artery does not anastomose freely with the cecal branches and is in reality an end-artery. Therefore, at the point of overlap, there is a relatively poorly supplied bank which he believes accounts for the sharp line of demarcation so often seen in gangrenous appendicitis.

In studies of the *position* of the appendix, both in cadavers and in the living, Trinca found that the position of the appendix varies with the location and degree of distention of the cecum, and that inflation of the cecum can produce torsion, kinks, and twists of the appendix. Since the appendiceal artery lies behind the distal portion of the ileum, distention of the cecum will tend to cause pressure on the artery with partial appendiceal ischemia.

Partial or temporary interference with the blood supply causes ischemia, followed by congestion or tissue stagnation of varying degree, and produces the phenomenon of so-called catarrh. In certain cases circulatory interference is sufficient to lower the resistance and thereby permits secondary invasion by any intestinal flora present. This process may be confined to the mucosa or extend through all coats and involve the peritoneum. A longer period of anemia produces gangrene. The portion of the appendix involved varies with the type of blood supply and the vessel obstructed.

If the obstructive process is of short duration, complete recovery can occur, but when it is of longer duration some damage is inevitable. Desquamating epithelium may not be restored. The

secondary inflammation may result in fibrosis, stenosis, atrophy, atonicity, and the formation of adhesions. It can pave the way for a subsequent attack of obstructive appendicitis or make a future attack more serious in its results.

*Perforation* may result from pressure gangrene due to a fecalith.

The author believes that aside from developmental anomalies, *chronic appendicitis* is due to conditions resulting from previous attacks of vascular disturbance, and not to a chronic primary infection arising in the mucosa.

*Purgatives* are aggravating factors as they cause increased peristalsis and cecal distention favoring torsion, kinking, and vascular disturbances.

In the author's opinion, modern *habits of eating and diet* are the predisposing factors.

Of 5149 appendices examined at the Peter Bent Brigham Hospital, Boston, in the past 20 years, *tuberculous appendicitis* was found by E. M. Drissen and R. Zollinger (Ann. Surg. 101:740 (Feb.) 1935) in 16 (0.3 per cent.). Of the patients with tuberculous appendicitis, 9 were females and 13 were between the ages of 15 and 30 years. In 12, the condition was of the ulcerative type. Perforation of a tuberculous ulcer may be the cause of an appendiceal abscess. In 4 of the cases reviewed the tuberculosis was of the hyperplastic type. This type of lesion is most readily diagnosed at operation, often by macroscopic examination, and offers the best possibility for preoperative diagnosis. The tumor is frequently palpable abdominally. In some cases it may be mistaken at operation for malignancy. The consensus of opinion is against primary infection of the appendix by way of the blood stream. As the cecum is often involved, the appendix is generally believed to become infected by direct extension and by infected contents.

The *ulcerative* or common type of *tuberculous appendicitis* usually shows no definite symptomatic pattern or distinguishing features to differentiate it from the ordinary acute or recurrent appendicitis. In 9 of the 12 reviewed cases of the ulcerative type the diagnosis of tuberculous appendicitis was not considered before operation. The cases in which a correct preoperative diagnosis was made are reported in some detail. In the 4 cases of hyperplastic tuberculosis of the appendix the condition was not diagnosed preoperatively and no other tuberculous focus was suggested by physical examination. Therefore, in 11 of the 16 cases the appendiceal lesion found at operation was the first evidence of tuberculosis discovered.

In summarizing, the authors emphasize that the preoperative diagnosis of tuberculosis of the appendix seems to depend on the presence of at least 2 of the following factors: (1) longer duration of the symptoms than in the average case of acute appendicitis without a fulminating course; (2) poor nutrition and loss of weight; (3) known tuberculosis; (4) diarrhea; (5) failure of the temperature to rise above 100.5° F. (38° C); (6) absence of vomiting; and (7) the presence of a tumor in the right lower quadrant of the abdomen. None of these is of any significance alone, but the presentation of several of them should suggest tuberculous appendicitis.

**Drainage** was employed in 5 of the 16 cases. Sinuses developed in 2 of the 5 cases in which primary drainage was employed and in 1 case in which drainage was not established at operation. The *prognosis* was poor in both types of the condition, but perhaps better in the hyperplastic than in the ulcerative type. Of the 11 patients with the ulcerative type, only 1 remained well. The follow-up information obtained in 5 cases operated upon recently was of little

value, as the length of time since the operation was too short to allow accurate conclusions regarding the end-results.

**Mortality.**—A survey of published statistics by L. L. Hobler (Ann. Surg. 103:86 (Jan.) 1936) reveals a wide variation in the mortality of appendicitis, depending upon the methods by which the type of cases was classified and the variations in the treatment. Mortality rates based upon vital statistics universally show an increase in the past 20 years. The Metropolitan Life Insurance Company has found that the mortality of acute appendicitis rose from 10.6 per 100,000 in the period from 1911 to 1914, inclusive, to 14.1 per 100,000 in the period from 1927 to 1930, inclusive, and estimates that in the United States there have been from 25,000 to 30,000 deaths annually from appendicitis in recent years, as compared with from 16,000 to 18,000 twenty years ago. In England, the Registrar General's statistics show that between 1913 and 1923 the mortality rose from 69 to 74 per 100,000. It is emphasized that these statistics are based upon the total number of deaths per unit of population, not upon case reports, and therefore do not indicate the incidence of the disease.

In 1934, Walker compiled comparative statistics from the literature for the periods from 1900 to 1915 and from 1916 to 1932. He found that in the latter period the general operative mortality was about 2.5 per cent. less than in the first period.

Hobler reviews 4791 consecutive cases in which appendectomy was performed at the Methodist Episcopal Hospital, Brooklyn, in the period from 1924 to 1934, inclusive. These included 2260 cases of acute appendicitis. He analyzes these cases in their various aspects, briefly summarizing the recent literature with regard to the points discussed.

Forty-eight per cent. of the patients were males and 52 per cent. females. Sixty-one per cent. of the deaths were those of males and 52 per cent. those of females. The patients ranged in age from 12 months to 80 years. Twenty per cent. were between 16 and 20 years and 72 per cent. between 6 and 30 years. The average mortality of the latter group was 1.8 per cent. Of the total number of deaths, 44 per cent were those of patients under 11 years or over 55 years of age, yet these patients constituted only 18 per cent. of the total number.

The 2 chief *preventable factors* in the mortality of acute appendicitis are *delay of operation* and the *use of cathartics*. The public must be taught that the ice-bag has no influence on disease, and that in cases of abdominal pain the administration of cathartics may be dangerous.

Among the *postoperative complications* in the reviewed cases the following are noteworthy:

Undrained cases: The formation of an abscess which necessitated secondary drainage, 4 cases; general peritonitis, 2 cases.

Drained cases: The formation of an abscess necessitating secondary drainage, 9 cases; fistula, 8 cases; and phlebitis, 10 cases.

In a study of acute appendicitis at the Presbyterian Hospital, New York, by R. N. Schullinger (Arch. Surg. 32:65 (Jan.) 1936) over an 18-year period prior to January 1, 1934, it was discovered that a considerable number of the case records were classified in improper subgroups. While these discrepancies change the mortality rate in the 5 main groups, they do not affect the actual number of deaths from acute appendicitis of all types. In the reviewed period the total mortality of acute appendicitis was 5.08 per cent., and the total death rate in each of the 5 groups

was as follows: acute appendicitis, 0.59 per cent.; acute appendicitis with acute local peritonitis, 1.0 per cent.; acute appendicitis with acute diffuse (diffusing, spreading) peritonitis, 17.02 per cent.; and acute appendicitis with progressive fibrinopurulent peritonitis, 88 per cent.

Each of the 5 types of cases of appendicitis is discussed in detail with an analysis of doubtful cases, a comparison of the mortality rates reported in the literature, tables, and graphs. Measures to lower the mortality in all types are suggested. The use of **spinal anesthesia**, **avertin with nitrous oxide**, or **local anesthesia** seems highly desirable. The importance of the **prevention of injury to the adjacent viscera** and of **gentleness in the manipulation of the appendix** to avoid rupturing it is emphasized. When difficulty is experienced in removing the appendix, it may be wiser simply to insert a **drain** down to it, because if removal is attempted there may be considerable damage to the stump of the meso-appendix and the retroperitoneal tissues, affording a means of extension of the infection and possibly producing pylephlebitis, retroperitoneal cellulitis, phlebitis of the retroperitoneal veins, or septicemia. If **enterostomy** is to be done, it should be performed **early** and not as a last resort. The administration of large amounts of **fluids**, repeated small **blood transfusions**, and **rest** should be included in the supportive treatment.

In cases with *peritoneal abscess* the attempt should be made to **drain** the abscess with the least possible trauma and by the simplest and quickest operative procedure. It is probably better not to approximate the subcutaneous tissues and the skin; these wounds should not be sewed tightly. Irrigation of the cavity with a surgical solution of chlorinated soda earlier than 5 days after the opera-



tion should be avoided because of the danger of disrupting the protective barriers and thereby causing sudden spread of the infection into the general peritoneal cavity.

In cases with spreading peritonitis and generalized fibronopurulent peritonitis, thoughtfully planned postoperative measures directed particularly against shock, distention, paralytic ileus, and toxemia are essential to lower the mortality rate. As the general surgical principles are the same in all groups of cases, they merit consideration by the surgeon who is anxious to use every possible means of reducing the mortality in the various groups.

The public should be taught that in cases of acute appendicitis in which operation is performed early by a competent surgeon at a well-equipped hospital the mortality is extremely low. Factors increasing the mortality are fear of hospitals and operations; the use of cathartics for abdominal cramps, "upset stomach" or "indigestion"; delay of consultation by the physician in doubtful cases; use of morphine and "freezing" of the appendix until life is jeopardized; and the "occasional operator" who so frequently is unable to cope with a difficult technical situation.

The curve of the 5-year average mortality in all types of cases of acute appendicitis shows a moderate general decrease. The 5-year average mortality curves for cases of Groups 1 and 2 show a decrease, but those of cases of Groups 3 and 4 show a definite, alarming increase.

**Cause of Death in Appendicitis.**—According to H. Doerfler (München. med. Wchnschr. 82: 1949 (Dec. 6) and 1996 (Dec. 13) 1935), death may be due to the mode of onset of the disease. An ulcerative lesion of the appendiceal mucosa may be in the process of develop-  
ment for days without the patient being

aware of it to the slightest degree. The destruction of the mucosa with progressive gangrenous involvement of the appendix may infect the adjacent lymphatic and venous channels, thereby leading to infection of the pararenal or subdiaphragmatic cellular tissues or of the neighboring Fallopian tube, or, by way of the blood stream, it may cause an insidious septic phlebitis (portal thrombosis). It is then too late for help without any fault of the patient or the doctor.

The author gives the following causes of death:

1. Peritonitis.
2. Improperly performed operation.
3. Hemorrhage from meso-appendix.
4. Septic portal thrombosis.
5. Septic phlegmon of the abdominal wall.
6. Intraperitoneal abscess.
7. Cardiac embolism.

**Treatment.**—INDICATIONS FOR OPERATIVE TREATMENT.—In his indication for operative intervention in acute appendicitis, W. F. Suermondt (Deutsch Ztschr. f. Chir. 247: 1 (May 18) 1936) is governed by the question of whether the inflammatory process manifests a tendency to encapsulation and not by the number of hours elapsed since the onset of the attack. A patient with an *acute spreading peritonitis* is submitted to an appendectomy regardless of the number of hours elapsed. The presence of *diffuse peritonitis* constitutes an even more stringent indication for operative intervention. On the other hand, a patient presenting himself with a sharply delimited inflammatory swelling in the appendiceal area even before 48 hours have elapsed is treated on a conservative plan. This consists of absolute rest in bed and in the Fowler position, strict diet and application of an ice bag. No attempt is made to differentiate sharply between an infiltrate and an abscess. The infiltrate may undergo complete

absorption, in which case the appendectomy is performed 6 weeks later. The inflammatory swelling, on the other hand, may continue to grow in size and to give rise to pain. The danger of perforation into the free peritoneal cavity is imminent if the *abscess* enlarges upward or mediad. Rise in temperature, onset of vomiting and muscle rigidity that did not exist before, constitute, together with the type of enlargement already described, an indication for immediate operative intervention. The abscess is incised and drained. No attempt is made to find or to remove the appendix. When the approach to the abscess is through the free peritoneal cavity, the latter is carefully protected with iodoform gauze, which remains undisturbed and is removed some time after the operation. An abscess pointing downward is treated conservatively in the Fowler position. It forms, as a rule, an abscess of the pouch of Douglas. Such abscesses according to the author, show no tendency to perforate into the free peritoneal cavity. They usually perforate spontaneously into the rectum, vagina or urinary bladder.

Treatment of appendiceal *peritonitis without drainage* is outlined by M. J. Krasnoselskiy (Vestnik khir. 40:193, 1935). His experience was gained by analyzing 1944 cases of acute appendicitis. He shares the view of many authors that the general peritoneal cavity cannot be drained and that, therefore, the drain is superfluous and at times injurious. If the appendix has been removed, the bleeding arrested and peritonization complete, there exist no indications for drainage. This postulate is not influenced by the character of the exudate, by the existence of gangrene or perforation of the appendix, or by the time elapsed since the onset of the attack. Local drainage with the view of isolating the focus of infection from the rest of the peritoneal cavity is indicated

in the presence of a suppurating area denuded of peritoneum, in failure to remove the appendix, in improperly carried out appendectomy, or in the presence of a raw, oozing surface. In a series of 950 cases of purulent appendicitis, 98 per cent. were closed without drainage. In a series of 360 cases of gangrene or perforation of the appendix, 67 per cent. were closed without drainage. The percentage of drained cases in a total of 1330 severe purulent appendicitis cases was 10.5. With regard to the character of the exudate, local drainage was practiced in 3.7 per cent. of the seropurulent type, in 30 per cent. of the purulent, and in 54 per cent. of the cases with abscess formation. Residual abscesses were less frequent when drainage was omitted. The incidence of abscess of the pouch of Douglas in the series in which drainage was not practiced was 3.3 per cent., while in the series in which it was practiced it was 7.8 per cent. Abscess on the left side was seen in 0.34 per cent. of the cases in which drainage was not done and in 2.16 per cent. of the cases in which drainage was done. There was only one case of subdiaphragmatic abscess, and that occurred in the drained series. Mortality in the series in which drainage was not practiced was 1.5 per cent., while in the other series it was 17 per cent. The analysis of the 12 fatalities occurring in the series in which drainage was omitted shows that only 7 patients died as the result of spreading peritonitis that was already present at the time of operation.

**APPENDICITIS IN CHILDHOOD:—*Diagnosis and Differential Diagnosis.***—After evaluating the early symptoms of appendicitis in children, E. L. Bauer (Pennsylvania M. J. 38:787 (July) 1935) states that the diagnosis of acute appendicitis should be made within 12 to 18 hours of its onset in order

not to expose the patient to the hazards of peritonitis or the sequela of abscess formation. It can be done without laborious laboratory assistance and by careful and prompt physical examination.

*Differential diagnosis* should include the elimination of the following conditions:

1. *Enteritis of Toxic Origin.*—The vast majority of cases, because of the onset of vomiting, are ascribed to dietetic indiscretions, and no further effort is made to find the true nature of the illness until it is too late. Either the child is immediately purged by its parents, or a laxative is ordered without proper physical examination. It is always incumbent upon a diagnostician to make his diagnosis at the patient's bedside and not his own. Although economies may make free telephone calls desirable rather than house visits, no child should ever be prescribed for without a physical examination. Enteritis, or simply gastritis, will not be accompanied by localized tenderness or rigidity to any marked degree. The temperature will be found at the higher levels with an almost immediate response. Enteric pain is generalized and spasmodic, and the diarrhea is typical.

2. *Intussusception.*—This abdominal catastrophe is more apt to be confused with enteritis than appendicitis. There is vomiting, pain, tenderness, and rigidity, a palpable mass by rectal if not by abdominal palpation, the typical bloody discharge, and the lashing peristalsis above the obstruction with ominous silence below. In view of the fact that the appendix is so frequently involved in this condition and prompt surgical interference is quite as imperative, no time should be wasted in a differential diagnosis of this kind.

3. *Ureteral Stone and Pyonephrosis.*—Since the pain and tenderness in young children in acute appendicitis is

located so far out in the flank, errors in diagnosis are apt to occur in so far as the urinary tract is concerned. Here the examination of the urine may throw some light on the possibility of infection in the kidney or its ureter. Pain may also be elicited over the deep kidney area, or a mass felt. Should the child be passing a stone, pain is apt to be paroxysmal, blood may appear in the urine, or the mass of hydronephrosis may be palpated.

4. *Pneumonia with Pleurisy.*—Ten per cent. of the children who have been referred to Bauer's clinic with a diagnosis of acute appendicitis have been found to have pneumonia with pleurisy. They have had pain referred to the abdomen as far down as McBurney's point. In these cases rigidity is false. With the rapid breathing of the child, a steady, firm, but slow pressure will find the palpating hand reaching well into any point in the abdomen without eliciting any definite point of tenderness. Incidentally, wincing is a better criterion of tenderness than subjective responses to questioning in the determination of tenderness.

The temperature in pneumonia very promptly rushes to higher levels; 103°, 104°, and 105° F. (39.4°, 40° and 40.5° C.) are not uncommon. Such a temperature range will be found only in the agonal stages in peritonitis with its classic picture that need not be described here.

The respiratory rate is increased, the alæ of the nose dilate with respiration, the cheeks are flushed, and the physical signs of pneumonia will be found in the right base or left apex in more than half of the patients.

In the other group, diminution in the breath sounds will generally be heard over certain areas in the lung, particularly in the right base. This may be due either to a thickening of the pleura,

a thin superficial layer of pneumonia, or both.

The popular notion that the pneumonia is "central" and therefore cannot be heard, is fallacious, for pneumonia so situated would obstruct the larger bronchial tubes and prevent the vesicular qualities arising in the more superficial lung tissue from manifesting themselves. This would lead to an easily recognizable deep tubular breathing.

Hyperresonance or slightly impaired resonance may be present. The leukocyte count is generally high. It must be emphasized, however, that the blood count is but a small part of the picture in the differential diagnosis of these conditions.

5. *Other types of Obstruction, Malformation, and Meckel's Diverticulum.*—These conditions so obviously demand immediate surgery that time should not be wasted in an attempt to differentiate them from appendicitis if there should be a doubt.

In the instance of a *long appendix* that early finds its way into the pelvis, the signs are transported to the lower abdominal wall and there may be evidence of either strangulated hernia, with the appendix as the culprit rather than the intestine, or the appendix may embrace the neck of the bladder, causing tenesmus and dribbling of urine, showing a distended bladder. In the female, symptoms referable to the internal genitalia are meager and unimportant because of the infantile character of these structures.

An attack of acute appendicitis may arise as the result of acute infection in any appendix. The malformations, because they interfere with the normal flow of blood through the organ and because the drainage through the lumen of the appendix may be interfered with, will be strong predisposing factors so that worms, fecal concretions, or foreign bodies may excite acute inflammation and infection.

Acute suppuration is more apt to follow acute infection. Gangrene may follow acute suppuration or result from an interference with the blood supply.

C. S. Stone, Jr. (Arch. Surg. 30:346 (Feb.) 1935) reviews 258 cases of acute appendicitis in children in which the diagnosis was proved by operation. The incidence of the condition reached a peak at the twelfth year of age and remained high during the following two years. The findings of this and similar studies indicate that there is a gradual increase in the frequency of acute appendicitis from infancy to adult life rather than a sharp increase at any one age period.

Acute appendicitis was found to be most frequent in children in the months of June, July, and August. As gastrointestinal disturbances are common at that time of the year, these conditions may be of importance in the etiology of the condition.

A definite history of one or more previous attacks of acute appendicitis was given in 64 of the cases.

The general clinical picture of the disease was found to be similar in children to that in adults. The distribution of cases in the 3 groups—Group 1, cases of acute appendicitis not ruptured; Group 2, cases of acute ruptured appendicitis, with localized peritonitis or definite abscess formation; and Group 3, cases of ruptured acute appendicitis with no localization of the peritonitis—was essentially the same in the two periods of life. The mortality in Groups 1 and 2 was the same in cases of children and adults, but in Group 3 the mortality in the cases of children was 34 per cent., whereas the mortality in the cases of adults was 16 per cent. The high figure in cases of Group 3 in children accounts largely for the difference in the total mortality, 7.75 per cent. in children and 2.9 per cent. in adults.

The high *mortality* in children is due to the lower resistance of the young to peritoneal involvement. It is obvious that reduction of the mortality can be accomplished best by early diagnosis and removal of the appendix before involvement of the peritoneum.

Of 140 cases of acute appendicitis in children reported by V. A. Shaak, (Vestnik khir. 40:99, 1935), 58 per cent. were in boys and 42 per cent. in girls. Acute appendicitis in children runs a more severe course than in adults and gives a higher mortality. The total in this series was 8.5 per cent.; for cases of later stages it ranged from 16 to 20 per cent. The younger the child, the more serious the prognosis, the mortality for those less than 3 years of age amounting to 20 per cent. The pathologic alterations in the appendix and in the peritoneal cavity develop with great rapidity, and perforation may occur earlier than 12 hours after the onset. The diagnosis in young children is difficult, and errors are more frequent than in adults. Pneumonia furnishes a high percentage of diagnostic errors. The operative indications are the same as in adults; the insistence on an **early operation**, however, must be even more urgent here because of the rapid progression of the process. The author advocates operative intervention in any stage of acute appendicitis, even after 48 hours, if the symptoms are not abating.

C. J. Baumgarten (California and West Med. 45:51 (July) 1936) maintains that the high incidence of 55 per cent. of perforated appendixes in children is due almost entirely to *delay*. He stresses that the medical profession should repeatedly remind the public of the possible danger of appendicitis in any ordinary so-called stomachache in children and persistently warns against the promiscuous use of laxatives before appendicitis has been definitely

ruled out. The frequent association of nasal colds, sore throats and middle ear infections is particularly misleading, and parents as well as physicians must realize that their presence with an abdominal pain does not necessarily rule out appendicitis. The use of the **continuous dextrose drip** in conjunction with the **indwelling nasal catheter** has been a distinct advance in the *postoperative care* of these children, not only in that it provides greater comfort, but also in that normal body chemistry is restored and toxins relieved in the quickest possible manner.

**ACUTE APPENDICITIS IN AGED.**—Of 1670 cases studied by F. S. Korganova and A. P. Krapivina (Klin. med., Moscow, 13:1142 (Aug.) 1935), 98.1 per cent. comprised patients ranging in age between 10 and 50, while 32 or 1.9 per cent. were past 50. The authors summarize their study of the 32 cases as follows: (1) The peculiarities of the clinical course of acute appendicitis in old people conditioned by the weak reaction of the organism. Persons with generalized arteriosclerosis react poorly or not at all to local inflammatory manifestations. Systemic reaction, as expressed by temperature and pulse, may be absent until the development of peritonitis. (2) The atypical picture of acute appendicitis of the aged is responsible for errors in diagnosis, late recognition, and a high incidence of complications. (3) **Operation** should be performed in all cases of acute appendicitis in the aged as soon as the diagnosis is established. Expectant treatment is permissible in the case of abscess. (4) Because of alterations in the cardiovascular and respiratory systems of the aged, the use of *general narcosis should be reduced to a minimum*. (5) The authors advise the removal of the appendix except when the presence of an abscess complicates the procedure. (6)

The incision is to be closed without drainage, except in the cases in which the focus of infection cannot be removed or in the presence of parenchymatous oozing from the bed of the removed appendix. (7) The postoperative treatment calls for especial attention to the status of the cardiovascular, the respiratory, and the intestinal tracts. (8) *Mortality* in the cases in which operation was performed in the early stage is not high (about 0.5 per cent.); in the late and the complicated cases it reaches from 30 to 50 per cent.

**GALL-BLADDER AND BILIARY TRACT.—CONGENITAL ANOMALIES.**—R. E. Gross (Arch. Surg. 32:131 (Jan.) 1936) has reviewed 147 cases of congenital anomalies of the gall-bladder collected from the literature and reports a case of double gall-bladder.

The occurrence in man of a *double gall-bladder* with 2 separate gall-bladder cavities and 2 cystic ducts has been reported 28 times. The 2 cystic ducts may subsequently converge and form a joint cystic duct which enters the common duct or they may empty into the extrahepatic biliary system separately. The accessory bladder may be found contiguous to the normal organ, under the left lobe of the liver, partially within the substance of the liver, or, rarely, along the gastrohepatic ligament. When the 2 gall-bladders lie next to one another, they are often invested by a common peritoneal coat. The duplicate nature of the organ is therefore occasionally overlooked at the operating table. The size of an accessory gall-bladder is usually approximately the same as that of the normal organ, but occasionally is only one-half or two-thirds as great.

The reports of cases of double gall-bladder do not mention any character-

istic symptoms or signs which might be of aid in the diagnosis of the anomaly before operation or autopsy. When the accessory organ is the site of inflammatory change or stone formation, the symptoms and signs are indistinguishable from those associated with cholecystitis or cholelithiasis in a normally formed gall-bladder. The mere presence of a second gall-bladder has not clearly given rise to symptoms in any case. The fact that most accessory gall-bladders have been found at operation and only a few at autopsy seems to indicate that the accessory structure is more likely to have pathological changes than the normally formed organ.

A *bilobed gall-bladder* in man has been occasionally described. This may have the form of a single organ divided by an internal central septum, but more often is V-shaped, with the 2 cavities joined only at their junction with the cystic duct. In the first type the septum is fibrous, but may contain smooth musculature. Glandular elements have been found in the septal mucosa.

A *diverticulum of the gall-bladder* may occur along the free surface of the organ from the neck to the fundus. In one case observed the diverticulum was found on the hepatic side of the gall-bladder. The diverticula vary from  $\frac{1}{4}$  to  $1\frac{1}{2}$  inches in diameter.

Thirty-eight cases of *absence of the gall-bladder* with no other anomaly of the liver or biliary system are listed. Not included in this review is a larger group of cases in which, in addition to absence of the gall-bladder, there was atresia of all or some portion of the hepatic or common duct system. Approximately 200 cases of atresia of the extrahepatic bile passages have been recorded in the literature. In about one-sixth of these the gall-bladder was absent. Absence of the gall-bladder has been found twice as frequently in fe-

males as in males. So far as could be determined from the reports, absence of the gall-bladder has no effect on the general health or the digestive functions.

An *hourglass gall-bladder* is frequently described. From most of the reports it is not clear whether the condition was or was not the result of inflammatory change and cicatricial con-

they have sometimes presented at operation. A normally formed gall-bladder has been found in the following anomalous positions: within the substance of the liver, under the left lobe of the liver, posteriorly under the inferior aspect of the right hepatic lobe, and horizontally in the transverse fissure of the liver.

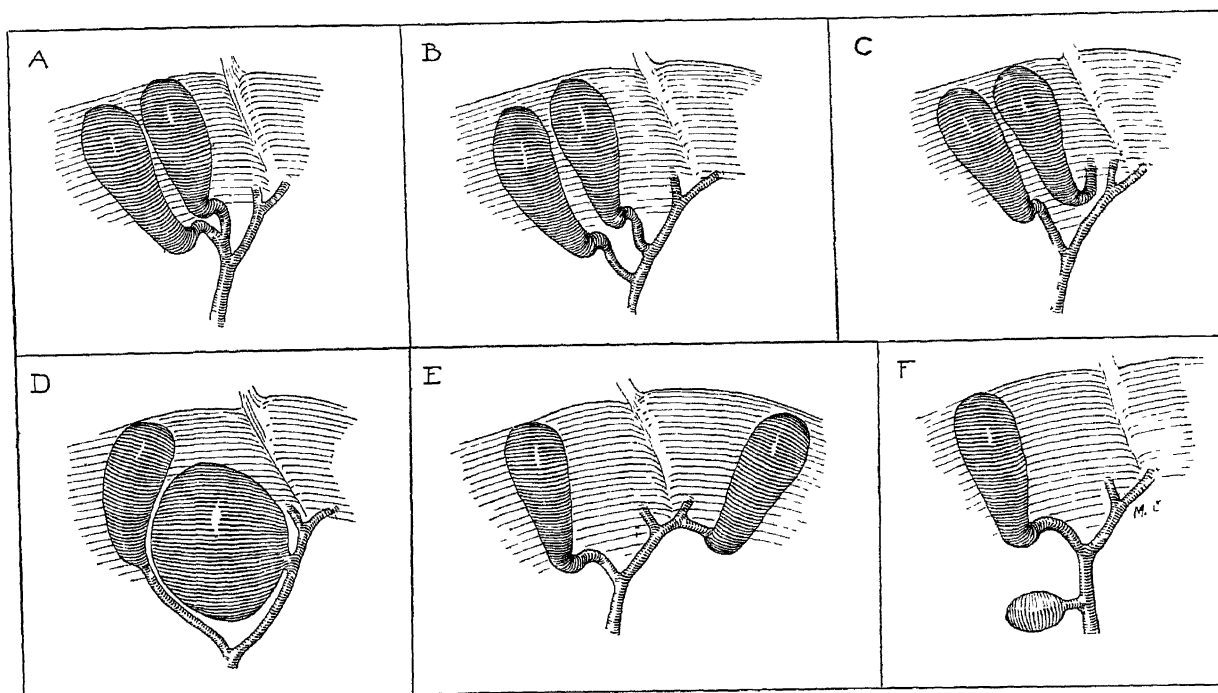


Fig. 1.—Types of double gall-bladder, showing position of accessory organs and distribution of their ducts. *A*, shows gall-bladder in normal fossa with Y-shaped cystic ducts; *B*, in the normal fossa with 2 separate cystic ducts; and *C*, in the normal fossa with an accessory cystic duct directly entering hepatic substance. *D*, shows an accessory gall-bladder partially embedded in right lobe of liver and communicating with main hepatic duct; *E*, an accessory gall-bladder under left lobe of liver and communicating with left hepatic duct; and *F*, an accessory gall-bladder in gastrohepatic ligament, communicating with common duct. (Gross: Arch. Surg.)

traction. However, hourglass gall-bladder has been found in young children in whom there was no evidence of gall-bladder inflammation.

Of interest to the surgeon, in spite of their apparent rarity, are those variations in the bile ducts in which accessory ducts enter the gall-bladder directly from the liver.

*Abnormal sites* of the gall-bladder are rare, but at least 4 such locations should be considered because of their interest to surgeons and the technical difficulties

\* A “floating gall-bladder,” because of its suspension by a “mesentery,” is likely to become twisted and infarcted. The resulting gangrene of the organ causes severe clinical symptoms and necessitates immediate operation. Surgical removal of the gall-bladder is followed by recovery in most instances if the operation is performed before peritonitis supervenes.

**Physiology.**—MOTOR FUNCTION OF GALL-BLADDER.—A review of various theories concerning the mechanism of

emptying of the gall-bladder and results of experiments on its motor function has been made by G. Zampa (Arch. ital. di chir. 40:389, 1935). In his experiments the gall-bladders of dogs were filled with iodized oil. Emptying was then initiated by the injection of pilocarpine and was studied by serial roentgenograms taken at intervals of 5 minutes.

1935), his bacteriological studies led to the conclusion that, in the average case of *biliary colic*, infection plays only a minor rôle. True ulceration of the mucosa is very rare when the gall-bladder is removed without trauma and is fixed before autolysis takes place. Thickening is caused in most cases by edema and takes place almost solely in

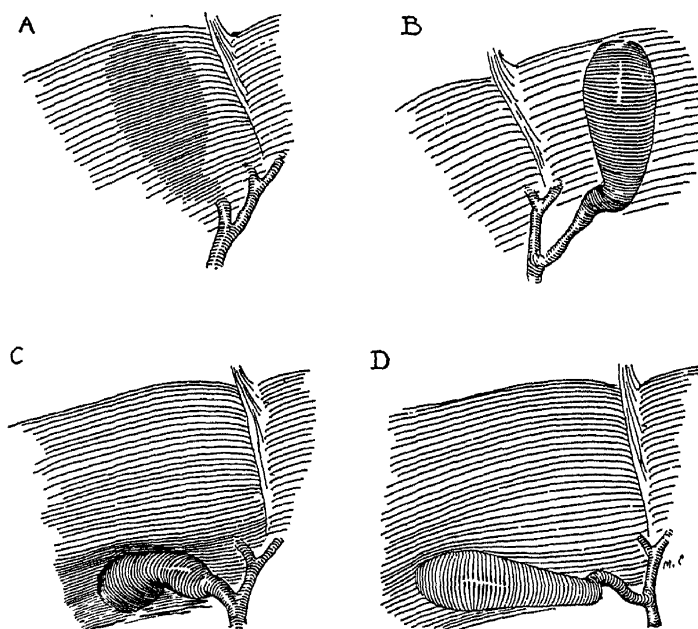


Fig. 2.—Abnormal positions of gall-bladder. *A*, in substance of liver; *B*, under left lobe of liver; *C*, on posterior part of inferior surface of right hepatic lobe; and *D*, horizontal, in transverse fissure. (Gross: Arch. Surg.)

From a study of the roentgenograms the author concludes that the gall-bladder empties itself by contraction of its muscular wall. The emptying is influenced by 2 factors: periodic opening of the cystic duct and contraction of the gall-bladder wall. There is a functional antagonism between the gall-bladder and the sphincteric mechanism of the cystic duct. The contraction of the walls of the gall-bladder is continuous, although slight, whereas the elimination of bile occurs rhythmically at short intervals, as a result of the periodic opening of the cystic duct.

**Pathology.**—According to E. Andrews (Arch. Surg. 31:767 (Nov.)

the subserous layers. In the reviewed gall-bladders, empyema, though diagnosed frequently in the operating room, was never found. Invariably the milky fluid proved to be either an emulsion of calcium carbonate or of amorphous or crystalline cholesterol. The one definite finding was that the degree of inflammation in the wall depended on the patency of the cystic duct. The new classification, which is based on this finding, is as follows:

*A.* Normal state of the gall-bladder:

Slight infiltration often seen; cholesterosis: presence or absence of stones. (The presence of these signs formerly often led to a diagnosis of chronic cholecystitis.)



*B.* Reaction to acute obstruction of the cystic duct:

Uncomplicated type (formerly called chronic cholecystitis).

Infective type (formerly called acute cholecystitis):

Empyema (?).

Type with vascular damage (formerly called acute cholecystitis):

Mild cholecystitis.

Ulcerative cholecystitis.

Gangrenous cholecystitis.

*C.* Reaction to intermittent obstruction of the cystic duct:

Normal condition between attacks.

Persistent irritation (usually mild).

*D.* Reaction to chronic obstruction of cystic duct:

Uncomplicated type (formerly called chronic cholecystitis).

Acute re-infection:

Mild.

Empyema (?).

Hydrops.

*E.* Reaction to obstruction of the common duct:

Acute or recent type (dilated and thin-walled gall-bladder).

Chronic type (shrunken and fibrosed gall-bladder).

*F.* Neoplasms.

On the basis of the clinical course, F. Zanardi and A. Previtera (Arch. ital. di chir. 42:273, 1936) recognize a *chronic* and a *subchronic* type of *cholecystitis with stones*. This classification conforms well with the results of functional tests, the histological findings in the liver, and the postoperative course. In the purely *chronic cases*, characterized clinically by dyspepsia, gastralgia, and colic, and the absence of fever and icterus, the hepatic lesions involve predominantly the interstitial tissue. A chronic inflammation, fibrosis of Glisson's capsule, and a hypertrophy-hyperplasia of the endolobular reticulum are found. The parenchymatous lesions are always negligible and confined to circumscribed foci. As they are usually not severe, the functional capacity of the liver is reduced only slightly, if at

all. The authors found also that the fibrotic and atrophic changes seen in biopsy sections taken from the liver margin tend to exaggerate the severity of the condition and may confuse the diagnosis.

As the results of operation are always good from the clinical as well as the functional point of view, the authors conclude that the hepatitis encountered in connection with chronic cholecystitis with stones is of minor importance.

In *subchronic cholecystitis*, on the other hand, the clinical course and the results obtained by cholecystectomy are rather unsatisfactory. This is readily explained by the findings of anatomical, functional, and surgical studies. The lesions involve the gall-bladder and surrounding structures, and there is a peculiar form of hepatitis which is characterized by a periportal lymphangitis, perihepatitis, and cholangitis. The functional capacity of the liver is definitely reduced, and the digestive disturbances and functional alterations tend to persist after operation. These facts suggest that in such cases, under the influence of an infectious factor (lymphatic or biliary inflammation), a hepatitis may become progressive quite independently of the gall-bladder involvement.

The authors subdivide cases of cholecystitis without stones into: (1) those of chronic cholecystitis; (2) those of adhesive pericholecystitis, and (3) those of appendicocholecystitis.

They conclude that cholecystitis with or without stones may be accompanied by a hepatitis which may be progressive. Adhesive pericholecystitis may run an independent course without involving the liver. Appendicitis may be associated not only with a demonstrable cholecystitis, but also with a mild and functionally not demonstrable hepatitis, suggesting that the liver may be attacked

in any toxic or infectious process occurring in the intraabdominal regions which drain into the portal vein.

**BILE SECRETION IN CASES OF BILIARY TRACT DRAINAGE.**—Following a discussion of the normal and pathological physiology of bile, E. Zilocchi (*Arch. ital. di chir.* 39:301, 1935) analyzes the composition and quantity of bile as affected by various physiological and pathological processes and then reports a study he made of the bile secretion of 7 patients. In all of the latter the bile was deviated out of the intestine. One of the patients had angiocholitis with empyema of the gall-bladder; 1, hepatogenic jaundice; 2, cholecystitis with stone; and 3, obstruction of the bile passages by a stone in the bile duct. All had had various operations for bile drainage. In 4 patients the drainage was total, and in 3 it was partial. The author collected the bile according to the method described by Berard and Mallet-Guy. He then determined its quantity, physical characteristics, content of mucus, content of bile pigment, and, in 5 cases, its daily content of cholesterin. The clinical, operative, and laboratory findings in each case are reported in detail. The general findings and the author's conclusions are summarized as follows:

1. In the immediate postoperative period the bile secreted was very dark. It remained that color for 5 or 6 days. There then began a period of transition during which the characteristics of the bile gradually become more stable.

2. In the second period, the period of transition, began the first variations in the daily secretion. These were slight in the cases of total derivation and more marked in those of partial derivation. They become progressively more marked as the bile assumed the characteristics of normal bile.

3. During the third period, in cases of total derivation, the bile secreted at

night was somewhat more concentrated than that secreted during the day, which showed the characteristics of true bile. In the cases of partial derivation, the bile secreted during the night had the character of biliary secretion, while that secreted during the day was a clear fluid with the appearance of gall-bladder secretion.

4. In the cases in which the determination could be made most accurately, the quantity of bile secreted in 24 hours varied from 400 to 750 c.c. In all of the cases the quantity of bile secreted on the first day was less than that secreted on the succeeding days, a fact which must be attributed to the action of the anesthetic on the liver. The hourly variations in the quantity of biliary secretion showed no appreciable rhythm. The maximum and the minimum amounts were found either during the day or during the night.

5. Investigation of the quantity of mucus in the bile showed very constant results. Determinations made under the most diverse conditions, in the bile secreted during the first and subsequent days, in bile removed by puncture of the gall-bladder, and in the secretion obtained by partial drainage, showed that the quantity varied from 2 to 4 per cent. This observation supports the theory of Landwehr that the greater density of the gall-bladder bile is due to the presence of a pseudomucin which is not precipitated by acetic acid. Only in some cases in the immediate postoperative period was there found a quantity of mucus greater than the normal, sometimes amounting to 20 per cent. This was believed to be due to an inflammatory condition of the biliary tract.

6. The quantitative variations in the bile pigments corresponded to the variations in the color of the bile. In the immediate postoperative period the

quantity of these pigments was high, especially during the first day, a fact due to the reduction in the secretion of bile and its consequent relative concentration in the first 24 hours. On the second day it rapidly decreased. Nevertheless, it still remained high for 5 or 6 days. At the end of that time there began a new decrease, corresponding to the period of transition, which terminated in minimal values. The considerable increase in the pigments in the immediate postoperative period depends upon: (a) the increase in their formation, due to the resorption of extravasated blood and the hemolysis caused by the anesthetic; (b) the anesthetic itself, which acts in two ways, decreasing the secretion of water and thereby causing a relative increase in concentration, and decreasing the elimination of pigments by the liver cells; (c) the elimination of pigments from the body in cases with jaundice; (d) the state of relative dehydration in the immediate postoperative period; and (e) the functional condition of the liver. In the period of transition there began hourly variations in the secretion of pigments, which persisted until the character of the bile became stable. In the cases of total derivation the variations were slight and consisted in an increase of the pigments during the night and a decrease during the day. In cases of partial derivation, they were fundamentally the same but much more marked, because in the secretion occurring during the day the pigments were very scarce, sometimes not measurable. These findings are explained by the action of the sphincter of Oddi which, when closed, caused the escape of bile from the drain and when open permitted its entrance into the intestine.

7. As regards the elimination of cholesterin the results obtained did not agree in the different cases. In 2 cases an increase in the cholesterin content

of the bile was found; in 1, a decrease; and in 2, a normal quantity. The findings seemed to show that neither the ingestion of food nor starvation has an influence upon it, since during starvation continued for several days after operation a decrease was found in only 1 instance. Moreover, the fact that the cholesterin in the blood was increased in these cases suggested that cholesterin is not formed in the liver, but is merely eliminated by it. The hourly variations in the cholesterin had no relation to the ingestion of food or fasting.

8. The observations made in the immediate postoperative period are indicative of a general disturbance of the secretory function of the liver, due to the operation and the anesthetic.

9. This period was followed by a longer period of varying duration during which the hepatobiliary function was gradually reestablished. In some cases it became entirely or nearly normal, whereas in others the improvement did not progress beyond a certain limit.

CHOLESTEROSIS OF GALL-BLADDER.—A. Moratti (Clin. chir. 11:357, 1935) reports 2 series of experiments on animals in which he demonstrated: (1) the absorption of thorium from the gall-bladder and the distribution of the lymphatics of the gall-bladder and liver; and (2) the development of cholesterosis of the gall-bladder following lymphatic stasis.

In the first series of experiments he introduced a solution of Chinese ink and thorium into the gall-bladder and after varying periods sacrificed the animals and studied the gall-bladder and liver with the x-rays and histologically. No evidence of absorption of the ink was found. On the other hand, the thorium salt was absorbed and granules of thorium were found in the lymphatic spaces and vessels of the gall-bladder wall and in the Kupffer cells of the liver. In the

subserosa and submucosa the thorium granules outlined two well-developed lymphatic networks which were connected by lymphatic vessels across the muscular layer.

In the second series of experiments lymphatic stasis of the gall-bladder was produced by dissecting the organ free from the liver and cutting the lymphatic trunks around the cystic duct. One week after the production of the stasis extensive desquamation of the epithelium, infiltration of the wall with blood or leukocytes, and a marked dilatation of the lymphatics, especially in the subserosa, were observed. The sudanophile granules were decreased in number in the epithelium, but appeared to be increased in the lymphatic reticulum of the subserosa and submucosa. The granules were found either free in the lumen or in the endothelial cells.

During the third week a regeneration of the epithelium, development of villi, accumulation of fat in the epithelium, and an increase in the fat granules in the subserosa and submucosa were found.

In the fourth week, macroscopic examination disclosed yellowish granules in the mucosa of the gall-bladder and histological examination showed the epithelium to be covered with numerous elongated villi. There were no signs of inflammatory infiltration. The fat granules were scarce in the epithelium but abundant in the subserosa and submucosa of the newly-formed villi. The fat was found either in large accumulations, free in the lymphatic vessels or phagocytized in the endothelial cells.

Examination 3 or 4 months after the surgical procedure showed a grossly and microscopically normal gall-bladder with adhesions to the under-surface of the liver. This demonstrates the reversibility of cholesterosis of the gall-bladder after reestablishment of the lymphatic

drainage of that organ secondary to the formation of postoperative adhesions between the gall-bladder and liver bed.

In the experimental production of cholesterosis of the gall-bladder by L. M. Rousselot and L. Bauman (Surg. Gynec. and Obst. 61:585 (Nov.) 1935) a gross pathological lesion was produced in every experiment that closely resembled the human picture of cholesterosis. When solutions of cholesterol are placed in the gall-bladder of a dog, there is consistent loss of the lipoid averaging about 50 per cent. in 24 hours. No apparent increase in the free cholesterol content of the gall-bladder wall could be demonstrated. The authors conclude that with the evidence produced, the absorption of cholesterol by the gall-bladder mucosa is suggested.

In a study of 600 cholecystectomies performed during the period between 1925 and 1935, A. Troell (Arch. f. klin. Chir. 185:211 (June 3) 1936) found 3 cases of so-called *lime bile* and 23 of *cholesterosis or strawberry gall-bladder*. Besides the stones, the gall-bladders in the first group contained an amorphous, putty-like substance the color of which was like that of the stones. This "lime bile" was possibly the forerunner of the stones. Of the 23 cases of the cholesterosis group, 19 presented stones. In 7 of these there was present a solitary stone made up entirely, or almost entirely, of cholesterol. In 2 cases large cholesterol stones were associated with smaller stones. In 5 there were found small mulberry stones the chief component of which was cholesterol. On gross inspection these gall-bladders presented a fine white or yellowish white structural network above the mucosa. It gave the impression in one of the cases of incrustated cholesterol. In 2 cases the reticulated mucosa showed prominent, yellowish white nodes in its entire extent. In 1 case, formations re-

sembling pedunculated papillomas were observed. Microscopic examination revealed chronic inflammation in 18 and acute inflammation in 3 of the cases. Deposition of cholesterol was the characteristic feature. In the subepithelial connective tissue layer there were clusters of large, clear round or polygonal phagocytic cells with a small nucleus, containing fat and giving the cholesterol reaction. The source of cholesterol in strawberry gall-bladder was believed by some observers to be the result of secretion by the mucous membrane, while others, notably Aschoff, held that its source was the gall-bladder bile, from which it was absorbed by the mucosa. By analogy with the stones of "lime bile," one is tempted to conclude that cholesterosis represents the first stage in the formation of cholesterol stones. Further observations will be necessary before this hypothesis can be accepted.

**CHOLELITHIASIS.**—The genesis of gall-stones has been studied by H. L. Bockus, J. H. Willard and H. N. Metzger (Pennsylvania M. J. 39:482 (Apr.) 1936). The authors analyzed the clinical and laboratory data that could be considered pertinent to the genesis of the common types of calculi and 156 cases of proved gall-stone disease. The cases have been segregated into 3 groups, depending on stone types: pure radiate cholesterol stones, calcium bilirubinate-cholesterol (mixed) stones, and pigment stones. A comparison has been made between the observations in the first two groups, particular attention being paid to an analysis of factors bearing on infection and disturbed cholesterol metabolism in gall-stone genesis. It is concluded that gall-bladder infection and cholecystitis probably do not play an important part in the genesis of the common mixed stone. Associated infection is more commonly observed in the calcium bilirubinate-cholesterol stone

group than in cases of the pure radiate cholesterol stone. Evidence is given which suggests that the concomitant inflammation of the gall-bladder so frequently encountered results from rather than causes the deposition of stones. A mobilization of all available information fails to establish the mechanism by which a disturbance of cholesterol metabolism is responsible for the deposition of cholecystic calculi. However, the data submitted suggest that an alteration in cholesterol metabolism plays an important part in the genesis of both the pure cholesterol and the ordinary mixed gall-stone.

I. Pavel (Presse méd. 43:1565 (Oct. 9) 1935) advances several arguments which militate against the generally accepted concept that stasis is a necessary prerequisite to the formation of gall-stones. There have been numerous cases of prolonged biliary stasis, confirmed by operation necropsy, without any development of stones. Furthermore, recent studies of icterus from functional stasis due to spasm of the sphincter of Oddi have shown that it does not favor the formation of calculi. Cholecystography has furnished additional evidence of this view. There are numerous instances in which atony of the gall-bladder has been found without any stones. On the other hand, vesicles have been seen showing normal contractile powers, but nevertheless containing stones. The author feels that all these observations tend to prove that the classic idea of stasis should no longer be accepted uncritically.

A microchemical study of biliary calculi has been made by T. W. Ray (J. Biol. Chem. 111:689 (Nov.) 1935). The author analyzed a large number of human biliary calculi and found that there is no essential quantitative chemical difference between the two types referred to as cholesterol-pigment-cal-

cium stones and cholesterol-pigment stones. Hence, there is no quantitative chemical basis for the present classification of these two varieties. Some cholesterol-pigment-calcium stones were found to contain even more cholesterol and less mineral matter than do some cholesterol-pigment stones. Some stones of supposedly opposite varieties, when analyzed, proved to be remarkably alike. There is a surprising regularity in the way the constituents are deposited in some stones, but, as a rule, these substances are laid down without order. Stones from the same gall-bladder were found to be very similar from a chemical standpoint. By using modern microchemical methods the author has made quantitative chemical measurements on calcium, iron, phosphorus and manganese. Quantitative determinations on the water-soluble substances of some stones are presented.

**CHOLESTEROLEMIA IN GALL-STONE DISEASE.**—A. G. Gukasyan and E. I. Antonova (Klin. med. 14:646, 1936) studied the blood cholesterol in 171 pregnant but otherwise normal women, of the ages between 18 and 35, in 9 women during the second, the seventh and the ninth month of pregnancy, as well as 2 months after delivery. They draw the following conclusions: The first attacks of gall-stone colic coincided with pregnancy in 35 per cent. Hypercholesterolemia is present in the greater portion of the gall-stone cases. Blood cholesterol increases with the advance of pregnancy and returns to the normal level 2 months after the delivery. This increase is the result of functional alteration of liver cells, due to initial intoxication of pregnancy. Since the placenta is impermeable to cholesterol, its presence in small amounts in the blood of the newborn speaks for possible synthesis of cholesterol in the organism. Cholesterolemia developing in parenchy-

matous alteration of the liver is caused by the loss on the part of the liver of the capacity for retaining cholesterol. Alterations in the liver observed in gall-stone disease are of a primary character and are the cause of hypercholesterolemia in cholecystopathies. Hypercholesterolemia in itself cannot cause gall-stone disease.

The pathogenesis of calculosis of the liver is discussed by G. M. Giuliani (Arch. ital. di chir. 39:61, 1935). The author concludes that one of the causes of the condition is an excess of cholesterol in the gall-bladder bile due to hypercholesterinemia. In studies of the gall-bladder bile in 2 cases of *strawberry gall-bladder* he found the content of cholesterol to be 8 and 10 parts per 1000, an amount much higher than the normal. When the patients were reëxamined 6 and 7 years after cholecystectomy, the amount of cholesterol in the bile extracted by sounding of the duodenum was only 1 part per 1000.

In experiments carried out by Giuliani on dogs, stasis of the gall-bladder was produced by fixing the gall-bladder to the duodenum. This resulted in strawberry gall-bladder, the formation of calculi, and an increase in the amount of cholesterol in the gall-bladder bile. Calculosis and strawberry gall-bladder, with excess of cholesterol in the gall-bladder bile, can be produced by injecting colon bacilli into the gall-bladder with or without fixation of the gall-bladder to the duodenum.

From clinical observations and chemical and experimental research the author concludes that stasis and infection are important factors causing an excess of cholesterol in the gall-bladder bile accompanied by strawberry gall-bladder and cholelithiasis, and that therefore *cholecystitis* with or without stones should be treated by **cholecystectomy**.

The relation of inflammation of the gall-bladder to concomitant pathological changes in the liver is still a subject of controversy. While some believe that cholecystitis is the result of hepatitis, others are of the opinion that the hepatic changes are secondary to the disease of the gall-bladder, and a third group hold that inflammation of the gall-bladder and pathological changes in the liver are independent of each other.

R. Colp, H. Doubilet and I. E. Gerber (Ann. Surg. 102:202 (Aug.) 1935) report a study of the relationship of disease of the gall-bladder to disease of the liver, with special reference to the finer cytological changes in the liver. Sections of liver taken from deep within the organ were studied in order to obviate the criticism that sections from the surface cannot be taken as an index of changes occurring throughout the organ. The gross pathological changes in the liver, gall-bladder, and bile ducts were carefully noted at operation. The gall-bladder was aspirated and retrograde cholecystectomy was done when indicated. After its removal, the gall-bladder was fixed by filling it with formalin and then cut longitudinally. Sections were studied with the finer staining methods. Specimens of liver were taken from the dome of the right or left lobe with the Hoffman biopsy punch at a depth of about 3 cm. Over 100 specimens were thus obtained with no untoward effects traceable to the procedure.

The authors attribute great importance to changes in the mitochondria in the cells studied. The mitochondrial stains were found more reliable in the demonstration of cell degeneration than hematoxylin and eosin.

In 40 cases of *cholecystitis*, acute and chronic, in which jaundice was not present at the time of operation, no changes in the liver parenchyma were found by

the finer cytological studies. The hepatic changes in this type of case reported by many were not demonstrated. However, in a series of cases with jaundice due to obstruction of the common duct by stone, 1 case of acute cholangitis, and 7 cases of obstructive jaundice due to a malignant tumor of the biliary tract or the head of the pancreas, the process of cell destruction could be verified by the alterations of the mitochondria. The changes were observed only in the vicinity of the bile capillary thrombi and were due to changes incident to obstruction. They bore no relationship to the changes occurring in the gall-bladder. The extensive necrosis of liver cells reported by some observers was not observed in this study.

**BACTERIAL CHOLECYSTITIS.**—The experimental studies of H. G. Aronsohn (Am. J. Surg. 32:18 (Apr.) 1936) were carried out over a period of 36 days with streptococci, staphylococci, the colon bacillus, and the bacillus welchii.

As a rule, the bacteria were introduced into the gall-bladder under ether anesthesia through a catheter inserted through the common duct, but in a few instances bacterial suspensions were injected through the gall-bladder wall.

The results showed that in a non-traumatized gall-bladder it is difficult to produce cholecystitis by the introduction of virulent bacteria, but in the presence of stasis of the bile (produced by ligation of the cystic or common duct) or of trauma to the gall-bladder wall, severe infection occurs with considerable constancy.

**ACUTE CHOLECYSTITIS.**—Three cases of acute cholecystitis associated with the presence of pancreatic ferments in the gall-bladder bile are reported by R. Colp, I. E. Gerber and H. Doubilet (Ann. Surg. 103:67 (Jan.) 1936). In 2 cases there was a nonperforative bile peritonitis.

It has been shown that if the papilla of Vater is obstructed by a stone, edema, or spasm, the common bile duct and the duct of Wirsung may be converted into one continuous channel and bile may then flow into the duct of Wirsung or pancreatic juice may flow into the chole-dochus. The intraductal pressure probably determines the direction of the flow.

If the pancreatic ferments reach a sufficient concentration in the gall-bladder to render the usual acid reaction alkaline, the bile salts may act destructively on the gall-bladder wall together with the activated pancreatic ferments. As a result of the chemical inflammation caused by these various factors, either an acute cholecystitis or nonperforative biliary peritonitis may develop.

**TUMORS OF GALL-BLADDER.**—*Papillomas* of the gall-bladder have been studied by A. B. Kerr and A. C. Lendrum (Brit. J. Surg. 23:615 (Jan.) 1936). They conclude that these lesions fall into 3 groups: (1) simple villous papillomas; (2) simple villous papillomas with transplantation; and (3) villous papillomas with malignant transformation. The Paneth cell, goblet cell, and enterochromaffin cell and their staining reactions and relationship are discussed. The authors report a case of chloride-secreting papilloma of the gall-bladder, in which operation cholecystostomy yielded 20 ounces of clear fluid, 10 ounces of thick dirty fluid, and 8 opalescent stones with bile pigment and calcium centers and an outer coating of cholesterol. Cholecystectomy appeared to be contraindicated because of the patient's condition. Following the cholecystotomy, large amounts of fluid poured out of the wound. In the 24 hours immediately following the operation, 38 ounces of thin fluid drained from the gall-bladder. Thereafter the drainage continued as a clear colorless watery fluid. During the third day its

amount reached 60 ounces in 24 hours. The urine contained practically no chlorides. The fluid from the wound contained sodium chloride at a concentration considerably higher than that of the blood plasma. Dehydration and chloride depletion resulted within 5 days and were successfully treated by the intravenous administration of saline solution. Later the gall-bladder was removed, but the patient died.

Examination of the gall-bladder disclosed a cauliflower-like growth 3 cm. high, in the region of the neck. The tumor consisted of 3 main masses and numerous closely adjacent polyps. On section, the tumor was found to be a simple papilloma of the gall-bladder covered by epithelium which had the essential characteristics of intestinal epithelium, containing large numbers of Paneth cells, some goblet cells, and a few enterochromaffin cells. The source of the fluid was considered to be this intestinal epithelium. The most striking fact was that this tumor, not 3 inches in diameter, concentrated sodium chloride from the blood plasma and poured it out at such a rate as to produce gross dehydration and chloride deficiency. The specialized nature of the cells in the papilloma is believed to show that the tumor arose in an area of heterotopic intestinal epithelium.

*Carcinoma of Gall-Bladder.*—According to C. F. W. Illingsworth (Brit. J. Surg. 23:4 (July) 1935), the surgical importance of carcinoma of the gall-bladder, as a grave and generally fatal sequela of calculous cholecystitis, requires no emphasis. The condition is far from rare. At the Edinburgh Royal Infirmary it was found in 0.42 per cent. of the autopsies performed and in 2.8 per cent. of all cases of malignant disease treated during the last 16 years.

All observers agree that a large proportion of the cases are those of women.



and that the condition is most frequent between the ages of 50 and 65 years. Before the age of 40 it is rare.

The presence of embryonic rests has rarely been suggested as a *cause* of carcinoma of the gall-bladder except in connection with the uncommon squamous-cell epithelioma, and even this tumor can be explained more convincingly on other grounds. That simple papillomas bear an important relationship to carcinoma is highly improbable. However, there are rare cases of multiple papilloma which appear to form an intermediate link between the simple tumor and the papillary type of malignant growth. A definite relationship between gall-stones and carcinoma of the gall-bladder is very evident. The risk of the development of carcinoma in patients with calculous cholecystitis is great. From the clinical standpoint, therefore, the aim must be to prevent the occurrence of carcinoma by early operation for gall-stones. Since carcinoma may arise even after removal of the stones, the only certain method of prevention is cholecystectomy.

A recent summary of all of the literature on the experimental production of carcinoma of the gall-bladder which was made by Burrows indicates the need for caution in assessing previous experimental findings. The claims of certain investigators that they have produced carcinoma of the gall-bladder experimentally cannot be regarded as substantiated.

There are 4 principal types of carcinoma of the gall-bladder which may be distinguished from each other fairly readily by either gross or microscopic examination. These are: (1) scirrhus carcinoma; (2) papillary carcinoma; (3) mucoid or colloid carcinoma; and (4) squamous-cell carcinoma or epithelioma.

In the great majority of cases carcinoma of the gall-bladder spreads by direct invasion of the neighboring viscera and regional lymph nodes. It seldom disseminates to distant organs even in its terminal phase. Quite early, however, it invades locally and oversteps the limits of successful removal. The first organ invaded is generally the liver. Almost as frequently involved are the regional lymph nodes. In the later stages of the disease the peritoneum is quite often invaded. In some cases the omentum, duodenum, colon, and even jejunum are affected.

As carcinoma of the gall-bladder is almost invariably imposed upon a former cholecystitis, generally with gall-stones, there is usually a history of previous biliary disease. In such cases the symptoms are of the type generally associated with chronic cholecystitis—flatulent indigestion, pain below the right costal margin, and occasional attacks of biliary colic—and one or more attacks of jaundice may have occurred.

In typical cases of carcinoma of the gall-bladder the *symptoms* are pain, associated with anorexia, nausea, vomiting, and jaundice, and examination may reveal a palpable swelling under the right costal margin. In atypical cases, the symptoms may be due mainly to obstruction of the common duct, obstruction of the cystic duct, or secondary growths.

**Symptomatology and Diagnosis.**—The atypical symptoms of gall-bladder disease are classified by I. W. Held (M. Clin. North America 19:649 (Nov.) 1935) as follows:

1. Extraabdominal symptoms only: (a) shoulder pain, (b) vertigo, (c) cardiospasm, (d) angina pectoris, and (e) arrhythmia.
2. Intraabdominal symptoms pointing conspicuously away from the gall-bladder: (a) Gastric—secretory, sensory

and motor; and (b) colonic—secretory, sensory and motor.

3. Predominant symptoms of chronic pancreatic disease.

4. Metabolic disturbances.

5. Symptoms of general infection (cholangitis and cholecystitis lenta).

6. Functional disturbances without demonstrable pathological changes in the gall-bladder: (a) disturbances of biliary secretion, (b) disturbances of biliary absorption, and (c) disturbances of motility (dyskinesia).

Held discusses the manner in which gall-bladder disease masquerades under these various symptoms and presents illustrative cases.

*Shoulder pain* in gall-bladder disease is attributed to phrenic nerve irritation and is a true neuralgia. *Westphal's sign* is the presence of tenderness elicited by slight pressure over the right humero-clavicular joint. *Vertigo* with accompanying *nausea* and *vomiting* in gall-bladder disease is explained on the basis of reflex irritation of the vestibular branch of the vagus nerve.

In 2 cases of *cardiospasm* the symptoms were entirely relieved following the removal of a pathological gall-bladder. The most important controlling factor in the causation of *cardiospasm* was a reflex disturbance in the balance of the sympathetic nerves innervating the esophagus.

In a large group of cases, symptoms of *angina pectoris* which may sometimes simulate coronary thrombosis are outstanding, the gall-bladder symptoms being entirely in the background. According to one of the two theories advanced to explain these attacks, there is an associated disease, if only of minor degree, in the coronary vessels that is activated by gall-bladder infection. According to the other explanation, which is more plausible, there is a disturbance in the viscerosensory reflex. Irritation of the

spinal nerve due to disease in the gall-bladder is carried to the sensory plexus supplying the aorta and the coronary vessels, producing the pain of *angina pectoris*. Held quotes Head as follows: "When a painful stimulus is applied to a part of low sensibility in close central connection with a part of much greater sensibility, the pain produced is felt in the part of higher sensibility." *Cardiac arrhythmia* may be explained on the basis of gall-bladder infection affecting a locus minoris resistentiæ in the innervation of the heart or the mechanism of conductivity.

*Gastric secretory disturbances* may be either hyperacidity or hypoacidity, and are reflex in nature. As a rule, the gastric acidity is normal in gall-bladder disease. If it is disturbed, the tendency is usually toward hypoacidity. It is not the degree of acidity that is responsible for the symptoms, but the associated hyperesthesia of the mucous membrane. If the latter is prolonged, the patient becomes a gastric hypochondriac. Gastric motor disturbances due to gall-bladder disease are generally manifested by delay of emptying due to pylorospasm. Gastric atony is not a factor. In a small percentage of cases there may be hastened emptying. *Gastric pain due to pylorospasm* incident to gall-bladder disease is effectively relieved by *atropine*.

*Secretory and sensory changes in the colon* resulting from gall-bladder disease usually occur simultaneously and are manifested chiefly by vague abdominal discomfort, anorexia, constipation, reflex nausea and vomiting, and the appearance of a large amount of mucus in the stools. This *mucous colitis*, which is usually considered a neuropathic disease, may be regarded as an allergic phenomenon when it occurs in the presence of gall-bladder disease. There are records of cases in which the syndrome was cured

by the removal of a diseased gall-bladder. *Colonic motor disturbance* is usually manifested by severe constipation of a spastic nature. The colonic symptoms may be sufficiently severe to lead to a diagnosis of neurosis with functional constipation, the gall-bladder disease being entirely overlooked.

Chronic *co-affection of the pancreas* is present in from 10 to 30 per cent. of cases of gall-bladder disease, but because of the great functional reserve of the pancreas, it seldom causes symptoms. The diagnosis may be confirmed by determining a marked diminution of pancreatic ferment in the duodenal contents and the stools. Disturbances of carbohydrate metabolism may accompany gall-bladder disease. The author believes that removal of the gall-bladder has frequently prevented the development of acute hemorrhagic pancreatitis.

Cases of biliary disease may occasionally present symptoms of general infection and septicemia (*cholangeitis* and *cholecystitis lenta*). *Streptococcus viridans* may be isolated from the biliary drainage. The treatment is **cholecystectomy and drainage of the gall-bladder**.

There is a large group of cases in which the symptoms point to the biliary tract, but at operation no pathological changes can be demonstrated. The realization that functional disturbances of the biliary tract may give rise to severe symptoms is largely the result of physiological studies by Westphal and Ivy. Disturbances of function may be secretory, absorptive, or motor. Disturbances of secretion may be evidenced by an excessive secretion of mucus which may plug the cystic duct and cause hydrops of the gall-bladder. Disturbances of absorption of the bile by the wall of the gall-bladder may be due to chemical changes in the bile, resulting in the pre-

cipitation of bilirubin crystals with the formation of calculi.

The conception of *biliary dyskinesia* was developed by Aschoff and Bachmeister in 1909, although Krukenberg in 1903 had reported a case of gall-bladder colic in which neither stone nor infection could be demonstrated. Meltzer, applying the law of contrary innervation to the gall-bladder, concluded that contraction of the gall-bladder causes relaxation of the sphincter of Oddi, and suggested the use of magnesium sulphate to relax the sphincter and empty the gall-bladder. This was elaborated by Lyon, who developed the Lyon-Meltzer method of diagnosis and treatment of gall-bladder disease.

The animal experiments carried out by Westphal showed that biliary dyskinesia is purely functional and due to a disturbance of the sympathetic nerves controlling the motor function of the gall-bladder, the anterior portion of the sphincter of Oddi, and the papilla of Vater. In the human being, Ivy and Sundholm have experimentally demonstrated coördination between contractility of the gall-bladder and spasm of the sphincter of Oddi.

The author has found that functional disorders of the biliary tract may exist for a long time before producing any organic changes or may never bring them about. The dyskinesias are divided into the *atonic* type, due to failure of the gall-bladder to contract, and the *hypertonic* type, which is due to the contraction of the gall-bladder against a spastic sphincter. *Treatment* of the *atonic type* is directed toward stimulation of gall-bladder contraction by **pituitrin** and the use of **tincture of belladonna** or **magnesium sulphate** to relax the sphincter. In *hypertonic dyskinesia*, **magnesium sulphate** (50 c.c.—1½ ounces—of a 25 per cent. solution) should be introduced by **duodenal**

tube. Dilute **nitrohydrochloric acid** may bring about gall-bladder contraction by stimulating the elaboration of cholecystokinin.

Every attempt should be made to rule out organic gall-bladder disease before treatment of a functional disorder is begun. If biliary dyskinesia is the result of some other intraabdominal condition, the treatment should be directed toward the original disease. The gall-bladder should not be removed unless organic disease is added to the functional disorder.

With a view of approximating the diagnostic significance of the presence of *crystalline elements in the stomach lavage*, H. A. Rafsky (Am. J. Digest. Dis. and Nutrition 2:214 (June) 1935) studied a group of patients with and without biliary tract disease. Cholesterol and carbonate crystals, as well as calcium bilirubinate pigment, separately or collectively, were found in most of the patients with proved calculous or noncalculous cholecystitis. In these patients with biliary tract disease, who came to operation, the crystalline elements observed in the preoperative specimen of stomach lavage were found to be similar to the crystals seen in stones and bile removed from the gall-bladder at operation. The crystals were found more consistently and in larger quantities when the lavage was performed in the morning following an attack of biliary colic.

The presence of the crystals in the stomach lavage is due to the regurgitation of the bile into the stomach. In about one-half of the patients the contents from the gastric lavage was deeply bile-tinged.

Crystalline elements were found in the stomach lavage in patients with calculous as well as noncalculous cholecystitis. Of the patients in whom microscopic examination of the stomach lavage revealed many cholesterol crystals

together with abundant calcium bilirubinate pigment, cholelithiasis (including choledochlithiasis) was found in 97.1 per cent. of the patients.

Crystalline elements, to have diagnostic significance, should be present in the stomach lavage in appreciable numbers. Few or no crystals in the stomach lavage, however, do not rule out biliary tract disease, especially if the examination is made when the patient is symptom-free or if very large calculi are present in the gall-bladder. More than one lavage may be necessary before the crystals are recovered.

**CHOLECYSTOGRAPHY.**—E. A. Boyden (Am. J. Roentgenol. 33:589 (May) 1935) discusses the shape of the gall-bladder in 165 individuals who were subjected to 200 series of cholecystograms—each series consisting of a large number of cholecystograms made to determine the reaction of a presumably normal gall-bladder to one or more forms of physiological experimentation.

Thirty (18 per cent.) of these individuals showed marked kinking of the gall-bladder, either between the body and infundibulum (24), or between the body and fundus (6). The kinking between the body and infundibulum, presumably occurring early in development through extreme modelling of the fossa vesicæ felleæ, is believed to represent merely an accentuation of a minor variation of the normal pattern. The gall-bladder with *kinking* between the body and fundus, in which the fundus is fixed and folded, is identified with the "*phrygische Mütze*" of German pathologists, first described by Bartel in 1916. The author's study indicates that it is the most common congenital anomaly of the human gall-bladder. On the basis of new embryological studies this anomaly is subdivided into 2 main types: the concealed or retroserosal type, caused by aberrant folding of the epi-

thelial anlage of the gall-bladder within the embryonic fossa vesicæ felleæ; and the serosal type, caused by aberrant folding of the fossa itself in early stages of development of fetal ligaments, vestigial bend of the gall-bladder is fixed by the development of fetal ligaments, vestigial septa, or constrictions of the lumen following delayed vacuolization of the solid epithelial anlage. On the basis of physiological studies, the author rejects the current European theory that the folded fundus of an otherwise normal gall-bladder is a source of pain in the upper quadrant of the abdomen and therefore of indisputable clinical importance.

Cholecystography is reviewed by A. C. Mooney (Brit. J. Radiol. 8:403 (July) 1935) with regard to the rationale of its use, the technic, and its value as an aid in the clinical diagnosis of gall-bladder disease. Visualization in the living subject has widened earlier conceptions of the anatomy of the gall-bladder and permitted the demonstration of considerable variation in the position, mobility, shape, and size of the organ. It has advanced knowledge of its physiology by permitting the study of absorption phenomena, motility, and evacuation, and the effects of physiological factors, drugs, and foods on evacuation. It makes possible the demonstration of pathological processes resulting in disturbances of function and other changes, and reveals gall-stones which escape detection in plain films because of non-opacity.

The author discusses various pathological conditions of the gall-bladder and the cholecystographic findings associated with each. He calls attention to the relationship of hypotonic and hypertonic conditions of the duodenum and lesions of the cecum and appendix to abnormal findings in cholecystograms. Extraneous causes, such as impairment of liver

function, achlorhydria, delay in the emptying of the stomach, external pressure, and vomiting after the ingestion of the dye, may result in loss of concentration and render diagnosis difficult.

The interpretation of the cholecystograms is discussed with regard to complete absence of concentration, normal concentration with normal motility, deformity and diminished size of the gall-bladder, normal concentration with diminished motility, faint shadows, and cholelithiasis. The differential diagnosis and errors in diagnosis are considered in relation to simulation of the bladder shadow, gas shadows, calcified costal cartilages, renal calculi, calcareous glands, duct calcifications, adenoma, papilloma, and carcinoma.

In conclusion the author states that for reliable results, the examination must be made with great care and the findings correlated with those of other clinical procedures.

A standard method for the roentgenological reporting of cholecystograms is presented by R. McWhirter (Brit. J. Surg. 23:155 (July) 1935). The technic of administering the dye which is employed at the Mayo Clinic is outlined. It appears that the oral technic, if carefully carried out as suggested, yields results just as accurate as the best results obtained by the intravenous method. The dye must be given in sufficient quantity and in a readily absorbable form, and not on an empty stomach, but with fruit juices, preferably grape-juice. No fats should be taken before or with its administration.

The cholecystographic data at the Mayo Clinic for 1932, consisting of 732 cholecystograms, all checked by operation, are analyzed and the accuracy obtained in the various groups is shown. The terms "poorly functioning" and "nonfunctioning" are defined in terms of pathology.

Peptic ulcer of the stomach and duodenum apparently does not interfere with the filling of the gall-bladder.

The importance of realizing that a good cholecystogram does not rule out even extensive and serious disease of the liver has been demonstrated.

Delayed emptying of the gall-bladder should not be regarded as evidence of disease.

The deposition of calcium in the gall-bladder indicates that at the time it occurred the cystic duct was blocked. It does not necessarily indicate that the cystic duct is blocked at the time of the examination, since the patency of its lumen may have been restored. Calcified gall-stones are a more definite indication for operation than gall-stones which are not calcified.

**CHOLANGIOGRAPHY.**—*Technic.*—S. A. Robins and L. Hermanson (Surg. Gynec. and Obst. 62: 684 (Apr.) 1936) modify the technic of Mirrizi by injecting the radiopaque medium into the duct before it is disturbed and by substituting **hippuran** in place of iodized oil. They have used the method in 25 cases. The first roentgenogram failed to agree in only one case with the exploratory observations and check-up roentgenogram. In this instance the dye stopped abruptly at the ampulla and failed to enter the duodenum. The impression was that obstruction probably existed at the ampulla, but exploration and check-up roentgenograms revealed that the duct and ampulla were patent. In 4 instances the pancreatic ducts were visualized, and chronic pancreatitis, as evidenced by enlargement and hardening of the gland, was found on exploration. These patients continue to complain of symptoms in whole or in part, and the authors believe, therefore, that this observation is of prognostic significance. No untoward reactions have been encountered as a result of injecting hippuran into the bile ducts.

This procedure is intended to furnish information not available by any other diagnostic method in use at present. Since extremely small stones and so-called sand bile will not show on the roentgenogram, judgment as to what should be done in cases in which the evidence is not clear-cut will depend as heretofore on the clinical evaluation of the case arrived at after thorough diagnostic study. A complete study should not be omitted even if this method is to be employed. The only contraindication to this procedure is the presence of acute infection in the biliary tract. X-ray visualization of the bile ducts according to the technic described interferes in no way with the conduction of the operation. On the contrary, by providing the surgeon with visual evidence, it should be of considerable value. This is especially true in the case of common duct obstruction due to stone. With further experience it should likewise provide valuable information in such conditions as neoplasm of the bile ducts, neoplasm of the head of the pancreas, hepatic stone, cholangitis, diverticula of the bile ducts, internal biliary fistula and stricture.

N. F. Hicken, R. R. Best and H. B. Hunt (Ann. Surg. 103: 210 (Feb.) 1936) state that the injection of radiopaque substances directly into the gall-bladder and bile ducts gives an accurate x-ray picture of the condition of the biliary tract. It demonstrates whether the ductal system is patent or occluded; shows the position and number of calculi, the extent and location of strictures, and the functional status of the sphincter of Oddi; outlines fistulous communications; and demonstrates dilatation and sacculation of the bile ducts. It makes it possible to determine how long the biliary tract should be drained; confirms the patency of the common duct before the drainage tube is removed; and shows

whether or not cholecystectomy will decompress the entire biliary system.

The authors describe two *methods* of cholangiography—the *immediate* and the *delayed*. They use lipoiodine diluted to from one-third to one-half its original concentration with sterile olive oil to render it labile. They prefer stereoscopic roentgenograms combined with fluoroscopic studies. With the immediate method, in which the radiopaque oil is injected during the operation and roentgenographic observations are made while the patient is on the operating table, they have had but limited experience. Such a procedure is indicated particularly in the problem cases in which the diagnosis is questionable or the selection of the proper procedure is difficult.

The *delayed method* has a much greater range of usefulness. In this procedure the diluted lipoiodine is injected into a drainage tube sutured into the gall-bladder or biliary ducts at the time of operation or into a biliary fistula, and roentgenograms are then taken immediately. The exact outline of the biliary system is revealed. If any abnormalities are noted, serial roentgenograms are taken at 15-minute intervals until the diagnosis is established.

The authors observed no ill effects from use of the diluted lipoiodine in cases of acute cholecystitis, cholangitis, stricture, calculi, or pancreatitis.

By means of direct x-ray visualization of the biliary tract with radiopaque oils, R. R. Best and N. F. Hicken (Surg., Gynec. and Obst. 61:721 (Dec.) 1935) have been able to demonstrate in 4 patients that an increased tonus or spasticity of the choledochoduodenalsphincteric mechanism is capable of producing a mechanical obstruction, thus causing a retention of bile. The dyssynergia of the common duct sphincter may be independent of, or associated with, a generalized infection of the biliary tract, the

presence of stones, strictures, kinks or pancreatitis. The extirpation of the gall-bladder, the removal of the stones, the division of the stricture and the drainage of the infected bile ducts do not always overcome the spasticity of the sphincter, for in some cases it persisted after these operative measures. Physiologic evidence indicates that the choledochoduodenalsphincteric mechanism has sufficient contractile force to prevent the flow of bile into the duodenum, thereby increasing the intraductal pressure and causing pain and discomfort. Such a concept offers a rational explanation for occurrence of "gall-stone colic" in the absence of stones or infection and for the so-called hepatic neuralgia, and accounts for the persistence of gall-bladder distress in some cholecystectomized patients. A dyssynergia, or spastic dysfunction of the choledochal sphincter, provides an anatomic blockade of the common duct, resulting in a retention of bile. The stagnant bile becomes infected, and calculi are then precipitated. In such cases a cholecystectomy would not necessarily be curative, for following the removal of the gall-bladder, the intrinsic spasm of the common bile duct sphincter may continue. The 4 patients were studied by lipoiodine visualization for as long as 33 days following a cholecystectomy, and the sphincterismus still persisted. It is probable that the proper postoperative medical regimen, including those substances which relax the choledochal sphincter, such as atropine, magnesium sulphate or fats, would do much to correct the abnormal spasticity of the choledochal sphincter and thus tend to minimize the unsatisfactory results that sometimes follow cholecystectomies.

PERFORATION OF GALL-BLADDER. — A. L. d'Abreu (Brit. M. J. 2:1150 (Dec. 14) 1935) has observed free extravasation of bile 3 times in the last 116 cases of gall-bladder disease en-

countered in his unit at operation or at postmortem examination (cases diagnosed as cholecystitis but not confirmed by operation have been excluded). Free perforation occurs most commonly in the elderly. Inflammatory disease of the gall-bladder associated with calculi is undoubtedly the cause of the condition. Although extensive gangrene of the wall associated with empyema has occurred in some cases, it is by no means always present. Age is a factor of great importance in the etiology of free perforation. A characteristic syndrome does not exist: few cases appear to have been diagnosed before laparotomy; acute cholecystitis, perforated gastric or duodenal ulcer, acute appendicitis, acute pancreatitis and intestinal obstruction have been simulated on several occasions. The safest guide to correct diagnosis lies in ceaseless vigilance when acute cholecystitis is being treated expectantly, especially in elderly patients; a rise of pulse rate associated with an increase in the area of abdominal tenderness must not be neglected. When uncertainty exists about the condition of a patient being treated expectantly for acute cholecystitis, laparotomy is desirable. Perforation can occur in a patient confined strictly to bed and on a fluid diet, as in one of the reported cases.

**BILIARY PERITONITIS WITHOUT APPARENT PERFORATION OF BILIARY TRACT.**—This condition was first described in 1911 by Clairmont and von Haberer, who formulated the hypothesis that it was due to certain pathological processes not detectable by ordinary macroscopic examination. Since the report of Clairmont and von Haberer, several other cases have been recorded in the literature.

G. Bombi (Arch. ital di chir. 39: 425, 1935) reports 2 cases of this type of peritonitis. The first was that of a woman, 48 years of age, who for 20 years had suffered severe epigastric pain

which recurred usually during the fasting hours and was relieved by the ingestion of food. **Cholecystotomy with drainage** was followed by uneventful recovery.

The second case was that of a 56-year-old woman with a history similar to that given by the first patient. **Cholecystectomy** was done. On histological examination of the gall-bladder the mucosa at the site of a macroscopically visible herniation was found to be necrotic and to show retrogressive changes such as are usually observed in postmortem material. The submucosa was slightly infiltrated with lymphocytes, neutrophils, eosinophiles, and a few erythrocytes. The muscularis was of normal thickness, but the circular layer was made up only of a few bundles with an interrupted and irregular arrangement. The subserosa showed the presence of a large thrombus. This area had undergone inflammatory and necrotic changes, and at several sites showed an accumulation of bile pigment which proved that bile had passed through the wall. The serosa was markedly inflamed. The peritoneal mesothelium had been destroyed and replaced by a thick fibrinous layer. The nonherniated portion of the gall-bladder was essentially normal.

It appears that biliary stones, cholecystitis, trauma, and certain rare pathological conditions, such as carcinoma of the gall-bladder, are predisposing factors. In a few cases the bile was found to contain ferments of pancreatic origin as the result of some abnormality of the pancreas or its ducts.

With regard to the *pathogenesis*, the author states that there seems to be considerable doubt whether the filtration theory is correct. Many other suggestions have been offered, but the problem still requires further investigation.



The *symptoms* are identical with those of a diffuse peritonitis. A differential diagnosis is impossible. The condition is most often confused with peritonitis caused by a ruptured appendix or a perforating peptic ulcer.

The *prognosis* is poor unless treatment is given. The *treatment* is always surgical and should be instituted early. The operation of choice is **cholecystectomy** combined with **drainage** of the common bile duct, but **cholecystotomy** and simple **drainage** of the subhepatic region have also given satisfactory results.

**CHOLELITHIASIS.**—The gall-bladder or common bile duct was distended by R. Zollinger and E. Young (New England J. Med. 213:714 (Oct. 10) 1935) in 6 patients. Under a short gas-oxygen anesthesia or local infiltration of procaine hydrochloride the stones were removed from the gall-bladder or common duct, and a sterile balloon was inserted which could be distended and the pressure recorded. When the patient had recovered sufficiently from the anesthesia to answer all questions intelligently, the gall-bladder or common duct was distended. Distention of the gall-bladder produced a feeling of indigestion or deep epigastric discomfort without the usual pain referred to the back or discomfort in the right hypochondrium. Nausea and vomiting did not occur, regardless of the degree of distention. Distention of the common duct produced a more severe epigastric distress, but again pain was not referred to the back. Inspiratory distress was characteristic of distention of either viscus. The chief difference between distention of the gall-bladder and of the common duct was the occurrence of nausea and vomiting with the latter. The significance of these observations was then determined from a study of the clinical histories of 100 cases of cholelithiasis and chronic chole-

cystitis with a negative history for jaundice, 100 cases of acute cholecystitis, and 100 cases of proved stone of the common duct. The authors' observations, which showed that vomiting followed distention of the common duct, were in accord clinically, in that distention of the biliary ducts, as by a calculus, produced a high percentage of involuntary vomiting as compared with calculi within the gall-bladder. They believe that a calculus in the cystic or common duct in patients having pronounced involuntary vomiting should be considered in the group of indications for exploration of the common duct.

In a later contribution R. Zollinger (J. A. M. A. 105:1647 (Nov. 23) 1935) concludes that a true visceral pain exists and that inability to reproduce referred pain to the back adds weight to the argument that referred visceral pain is usually the result of inflammation, probably over a peritoneocutaneous radiation instead of a viscerocutaneous reflex.

**Treatment.**—The success of surgery of the biliary system depends on the physiological status of the liver. According to F. V. Hussey (Anesth. and Analg. 14:263 (Nov.-Dec.) 1935) the liver plays an important rôle in many vital functions such as: (1) the formation and storage of bile, fibrinogen and glycogen; (2) the excretion of bilirubin; and (3) the detoxification of poisonous chemicals. Disease of the biliary system impairs the efficiency of the liver. There are many tests for studying the degree of liver impairment which depend on some one physiological characteristic of hepatic function, such as the metabolic (galactose and cinchophen tests) and the excretory (bromsulphthalein and phenoltetraiodophthalein tests). Several of these functional capacity tests should be employed in the preoperative study of the patient. If the results show alteration in the sugar metabolism of the liver,

poor or slow excretion of hepatic dyes, or abnormal amounts of bilirubin in the blood, liver damage exists.

Liver function can be improved by the administration of **glucose** in the form of a rich carbohydrate **diet** or by **enteroclysis**. Glycogen thus made available stimulates the regeneration of liver cells, neutralizes toxins, and diminishes the danger of prolonged bleeding. It has been demonstrated experimentally that as much as 100 grams of liver tissue can be regenerated daily and that a 90 per cent. retention of dye for one-half hour will be decreased to retention of from 30 to 40 per cent. by glucose treatments in a period of 2 weeks.

The *hemorrhagic tendency* so frequently characteristic of biliary tract disease is an indication of impairment of liver function. The liver is the sole former of fibrinogen. Insufficiency of fibrinogen has an unfavorable effect on the coagulation time. It is possible also that a damaged liver yields abnormal amounts of heparin, which is an anticoagulant. Furthermore, calcium is removed from its active state in the blood by combination with abnormal amounts of bile salts and bile acids. **Calcium therapy** lessens the risk of hemorrhage only insofar as, combined with **glucose therapy**, it improves liver function. Direct **whole blood transfusions** should be given **preoperatively** to reduce the danger of hemorrhage.

*Myocardial damage* is often associated with disease of the biliary system. It is thought that the latter is a focus of infection of long duration with an inevitable effect on the heart. The status of the circulation and heart should be determined before operation. An electrocardiogram will reveal any myocardial damage. Careful investigation of cardiorespiratory symptoms is also essential. Râles at the bases of the lung indicate congestive failure. Routine **digitali-**

**zation** of the heart is not necessary in all cases; it should be done only **when indicated**.

The *anesthetic* employed should be the one which will be safest for the patient. It must not be toxic for the liver or further depress liver activity as does ether. It should be chosen and administered by a medical anesthetist (not a lay technician), but not until the complete case record and all laboratory data have been studied. In the author's opinion, **spinal anesthesia** is best suited to the majority of cases because its use is associated with minimal straining and smooth respiration and permits good exposure without producing deleterious effects on the liver. In cases which are poor risks, Hussey (*Ibid.*) gives premedication and uses **local anesthesia** and **splanchnic block** supplemented by **ethylene** or **nitrous oxide** or **cyclopropane**. After general anesthesia, hyperventilation of the lungs with **carbon dioxide** and **oxygen** considerably lessens the incidence of postoperative pulmonary complications.

There are two *complications* frequently encountered *after surgery* on the biliary system. The first is *hemorrhage* consisting of a constant ooze directly from the wound or from the gastrointestinal mucosa. As a rule, the use of hemostatics and calcium solutions is of no value. **Whole blood transfusions** given early and repeatedly will prevent exsanguination. The second complication is the so-called "*liver death*." This is characterized clinically by a rise in the temperature and pulse rate, anuria, and uremic manifestations. Autopsy shows extensive degeneration of the liver and renal parenchymas which are probably caused by powerful toxins. The treatment indicated in the presence of the described symptoms is the intravenous administration of concentrated **glucose**

solutions, the prevention of dehydration, and blood transfusion.

The article by B. Lipshutz (Ann. Surg. 101:902 (Mar.) 1935) is based on 20 consecutive cases of *acute cholecystitis* in which operation was performed within from 3 to 24 hours after the patient's admission to the hospital. In more than half of the cases the operation was done within 12 hours. In a few it was delayed for 48 hours for better preparation of the patient. The literature presents evidence demonstrating that it is often impossible to determine the extent of the inflammatory process in the gall-bladder or, especially in the aged, the presence of perforation by clinical examination.

Because of the possibility of perforation and other complications, such as peritonitis, ileus, and cholangitis, the author believes **early operation** is indicated. He states that early removal of an acutely inflamed gall-bladder should decrease the incidence of pulmonary complications, as the latter are dependent in part on reflex fixation of the diaphragm. Immediate operation is frequently contraindicated by advanced age, marked obesity, advanced cardiovascular disease, severe diabetes, and pulmonary tuberculosis.

**Cholecystectomy** is the operation of choice, unless the patient's condition permits only **cholecystostomy**. The latter is carried out in desperate cases and under only local anaesthesia.

Two methods for the treatment of *chronic cholecystitis* have been reported by E. Machline, V. Grigorenco and Z. Gorbounova (Presse méd. 43:1708 Nov. 2) 1935). The first is based on the idea of associating the antiseptic action of methenamine with the vagosympathetic action of calcium salts. The technic is simple: It consists in filling a syringe with about 5 c.c. ( $1\frac{1}{4}$  drams) of a 10 per cent. solution of calcium

chloride and 40 per cent. methenamine. The injections are made in the median basilic vein daily for 2 weeks. The dose is increased until 20 c.c. (5 drams) of the mixture is injected at a time. Fifteen patients were treated in this way. In general, the pain disappeared, the duodenal contents improved rapidly, the leukocytes, epithelial cells and mucus disappeared, the appetite returned and the patients gained weight. The second method of treatment consisted in using **gentian violet**. A 1 per cent. solution, carefully filtered, was injected intravenously in 10 c.c. ( $2\frac{1}{2}$  drams) quantities. The injections were also repeated daily. Of 19 patients treated in this manner, the response was good in all but one case. The explanation for the favorable action of these substances is not yet entirely clear, but the practical results were good.

The question of the **operative treatment** of the *strawberry gall-bladder* is discussed by F. Bernhard and E. Fenster (Deutsch Ztschr. f. Chir. 247:145 (June 22) 1936). The authors state that during the period between 1906 and 1935 there were 433 cases of strawberry gall-bladder in which operation was performed at the surgical clinic of the University of Giessen. Of these, 380 were in female and 63 in male patients. The age incidence was the same as that noted in cholelithiasis. Pain in the right upper quadrant and typical colics were the prominent symptoms in 380 cases. In 100 patients, jaundice was either present or existed at some time. In 100 cases, stones were present. Their composition differed from that seen in cholelithiasis. In 14 instances out of 24, sugar tolerance tests gave abnormally high sugar curves before the operation. Diastase determination in 29 patients before the operation demonstrated an increase in one-fourth of the cases. They have observed cases with a normal

blood sugar curve but with increased diastase or pancreatic lipase in the blood serum. The quinine-refractory liver lipase was frequently increased. In about half of the cases, either the external or the inner pancreatic secretion are therefore of value in the diagnosis of strawberry gall-bladder. Differential diagnosis from cholelithiasis and stasis of biliary tracts is difficult. Of the 443 patients, 11 died following the operation and 27 after leaving the clinic. Seventeen of the latter died of carcinoma. Two hundred and one patients replied to inquiries and 110 were reexamined. In 80 per cent. of the follow-up cases, relief of complaints was complete, while in 10 per cent. the operation was considered a failure. Subacidity and anacidity following the operation were observed with about the same frequency as after the operation for cholelithiasis. The frequent occurrence of alimentary glycosuria and the abnormal blood sugar curve, as well as the increase of the atoxyl-refractory blood lipase, point to the existence of a chronic pancreatitis, which the authors regard as the cause of postoperative complaints. Operative intervention, though justified, is not as urgent as in cholelithiasis. It is clearly indicated, however, in the presence of pain and colicky attacks. From present knowledge, the strawberry gall-bladder is to be regarded as an independent disease entity and in many cases as the forerunner of cholelithiasis.

The difficulty of treating an established *carcinoma of the gall-bladder* emphasizes the importance of preventing the occurrence of the condition by radical treatment of its main etiological factor, calculous cholecystitis, according to C. F. W. Illingsworth (Brit. J. Surg. 23:4 (July) 1935). When it is borne in mind that malignant disease is the eventual outcome in a large proportion of cases of gall-stones, it is evident that the benefits

of timely operation far outweigh the risks. The observation that carcinoma may develop years after the removal of stones by cholecystostomy indicates that the operation of choice for cholelithiasis is **cholecystectomy**.

In discussing malignancy of the gall-bladder, J. F. Erdmann (Ann. Surg. 101:1139 (May) 1935) does not include malignancy of the bile ducts or secondary or metastatic malignancy of the gall-bladder. On the basis of his experience in about 3000 operations on the gall-bladder he believes it is best not to induce patients to submit to gall-bladder operations by use of the cancer argument. He states that in employing this argument the surgeon must be certain that his operative mortality is less than the incidence of malignancy.

The author's records for a period of 5 years show 522 **cholecystectomies** and 3 **cholecystostomies** with 15 deaths, a mortality of 2.85 per cent. The incidence of malignancy was 1.14 per cent. (6 cases), less than half the mortality of operation. The average age of the patients with cancer was 48 years.

In all of the author's cases in which a carcinoma was discovered at operation for disease of the gall-bladder, a stone or stones or biliary sand was found.

Except in cases in which metastases are already present, there are no symptoms or signs upon which the diagnosis of carcinoma of the gall-bladder can be based with certainty. The treatment of choice for primary carcinoma of the gall-bladder is **cholecystectomy** when this is possible.

The **electrosurgical obliteration of the gall-bladder** without drainage is outlined by M. Thorek (Am. J. Surg. 32:417 (June) 1936). Experimental studies for a number of years have convinced Thorek that if a dry, nonleaking surface could be substituted for the dis-

charging cavity that the gall-bladder bed represents following cholecystectomy, it would be a great step in the right direction. This thought has been brought to fruition by electrocoagulation. If a flat electrode of bipolar current is firmly applied to a tissue surface and a current of proper voltage and sufficient amperage is permitted to pass through it, dehydration and coagulation of the tissue proteins results in a few seconds. On the other hand, if the same electrode is not applied firmly or if used as a unipolar or even bipolar instrument, a small air space (dielectric) intervenes between the electrode and the tissue, sparking, fulguration and carbonization with black discoloration of the tissues result. A re-application of the electrode to such fulgurated or carbonized surface will stop further current penetration and prevent coagulation from taking place. The author evolved his method of **cholecystelectrocoagulectomy** on the basis of experimental researches and clinical studies, the underlying principles of which consist of: (1) biterminal electro-surgical obliteration of the posterior wall and bed of the gall-bladder by electrocoagulation; (2) because of the great tendency of electrocoagulated surfaces to become agglutinated with serous surfaces, mustering of the falciform ligament into service by completely detaching it from the anterior abdominal wall; and (3) strict avoidance of drainage. Up to April, 1936, he has performed this operation in 181 consecutive, unselected cases of gall-bladder disease, including gangrenous, empyematous, sclerosed and other forms of pathologic disorders of the gall-bladder. There was one death. Postmortem examination showed that the patient died from causes unrelated to the operation. Kellogg used the method in 16 cases without a death, while Finlayson operated on 4 patients with good results. This brings the

total number of operations performed to 201 cases.

L. R. Whitaker (New England J. Med. 213: 596 (Sept. 26) 1935) reports the results in 16 cases in which **electro-surgical cholecystectomy** was done by the method described. In these cases there were 3 deaths, but none of the deaths could be definitely attributed to the use of electrosurgery. In 13 cases the operation was followed by uneventful recovery and the final results were satisfactory. Some of the surviving patients have been followed for 2 or 3 years.

The author states that when considerable coagulated tissue has been left in place, when there has been a pronounced inflammatory reaction, and when it has been impossible to tie the cystic duct securely, **drainage** is advisable. The drain used has been the soft rubber tube inserted into, or attached to, the stump of the cystic duct, or the rubber-dam cigarette drain (Penrose) with no exposure of gauze.

**OPERATION ON COMMON BILE DUCT.**—According to A. W. Allen and R. H. Wallace (Am. J. Surg. 28: 533 (June) 1935), primary surgery on the common bile duct is now an essential part of the treatment of gall-bladder disease rather than a secondary operation. Lahey reports that in his clinic the incidence of primary choledochostomy increased from 15.5 per cent. in 1926 to 42.5 per cent. in 1931.

Such procedures as dilatation of the papilla of Vater and duct by special duct catheters (Cheever, Bakes) and **irrigation of the duct into the duodenum** (McArthur, Matas) have been advocated as supplements to common duct surgery, but have not been practiced routinely.

Bakes recommends **gradual dilatation of the papilla** to the size of its common duct after incision into the

duct. He believes that this will improve the drainage of bile into the duodenum and allow the escape of any stone overlooked during the operation. He has devised for the purpose olive-tipped bougies ranging from 3 to 14 mm. in diameter. He states that such slow dilatation causes no formation of scar tissue.

The authors' technic is as follows:

*Technic.*—A right long paramedian incision is made, the rectus muscle retracted laterally, and the peritoneum opened. All adhesions are freed. The pancreas is carefully examined to exclude malignancy. The gall-bladder is decompressed by suction, and after visualization of the biliary ducts the gall-bladder is removed in the usual manner. Following decompression of the common duct by aspiration with a hypodermic syringe, the duodenum is freed for further exposure of the duct. The supraduodenal portion of the duct is incised in a longitudinal direction and 2 guy sutures are placed in each edge. The surgeon then goes to the left side of the patient and inserts the fingers of the left hand under the duct and the thumb above it. This enables him to milk out and remove any stones under direct vision. A probe is passed through the incision into the duodenum and followed by the Bakes dilators until sufficient dilation of the papilla is obtained. If the probe cannot enter the duodenum, the latter is opened longitudinally and retrograde dilatation is done. The duodenum is closed transversely. The dilatation is done slowly and gently to the widest diameter of the duct. During the entire procedure, the suction tip lies in contact with the operative field, aspirating oozing bile and any fine debris that may be spilled. A No. 10 soft rubber catheter is sewed into the lower angle of the wound with No. 00 chromic catgut on an atraumatic needle and the incision closed about the tube. After peritonealization of all raw surfaces, a gauze wick is placed in the subhepatic fossa. The gauze wick and the catheter are brought out through a stab incision made under the lower border of the twelfth rib. The abdomen is closed in the usual manner. The catheter and wick are removed on the tenth postoperative day. The authors emphasize that the gauze wick is placed in the subhepatic fossa and no drains are placed in contact with the gall-bladder bed, ducts, or duodenum.

Surgeons employing this technic report that their patients have a smoother postoperative convalescence with less vomiting, and that the incidence of duodenal irritation, infection, and incisional hernia is low. Probably the most important factor is the routine dilatation of the papilla.

The authors next discuss the *indications for exploration of the common duct*. These are:

1. Recurrence of symptoms following a cholecystectomy or choledochostomy. Patients who return with the same symptoms after a gall-bladder operation usually have some abnormality of the common duct. In many cases the authors have found a duct dilated by a stone and constriction of the papilla. The symptoms may be relieved by the technic described.
2. Jaundice of an obstructive type. Patients who show a progressively increasing or a stationary jaundice of an obstructive type should be subjected to duct exploration, with dilatation of the papilla after the usual preoperative preparation.
3. A history of chills and fever following biliary colic. In cases with these symptoms there is usually an inflammation of the duct system with the gall-bladder acting as a focus of infection. For such cases cholecystectomy and primary choledochostomy by the described technic rather than cholecystostomy is recommended.
4. A history of very frequent attacks of biliary colic.
5. The presence of small stones or sand in the gall-bladder.
6. Contracted gall-bladder.
7. Thickening in the head of the pancreas.
8. Cholangitis.
9. Impairment of liver function, due to mechanical interference with bile drainage into the intestine.

Of 901 operations performed for diseases of the gall-bladder and its ducts in the period from January 1, 1931, to November 1, 1934, 138 were cholecystectomies with primary choledochostomy and dilatation of the papilla. In the cases in which these operations were performed there were only 4 postoperative deaths. In 113 cases in which cholecystectomy was done with exploration of the common duct but without dilatation of the papilla, there were 8 deaths. Of the entire series of cases, exploration of the common duct was done in 269 (30 per cent.) and, of the latter, stones were found in the duct in 40 per cent.

The possible *complications* that may occur *after dilatation of the papilla* are duodenal reflux and acute pancreatitis, due to dilatation or injury of the transduodenal portion of the duct. Duodenal reflux or backflow of the duodenal contents into the common duct did not occur in the cases reviewed, but has been reported by other surgeons. Acute pancreatitis developed in 1 case. This may occur in any large series of cases and should not condemn the procedure.

The question as to whether the common duct should be drained by a catheter or closed immediately is important. Bakes advocated closure of the duct because of the hydraulic action of a closed system. However, he noted considerable bile drainage from the suture line in a large number of his cases. The authors believe that the dangers of biliary peritonitis are too great to permit absolute closure without drainage.

The *indications and the results of choledochoduodenostomy* are cited by G. Pototschnig (Deutsche Ztschr. f. Chir. 244: 288, 1935). Among 72 operations on the common duct, 18 choledochoduodenostomies were performed. The objections which have been advanced against choledochoduodenostomy were

refuted. In the surgery of the biliary passages the procedures of choice are those which permit internal drainage. Choledochoduodenostomy is to be considered when, after artificial dilatation of the papilla, simple suture of the common duct is either impossible or untrustworthy. Other indications for this procedure are:

1. The presence in the common duct of multiple calculi with an admixture of mucus and grit.
2. Cicatricial narrowing of the lower portion of the common duct and chronic cirrhosis of the head of the pancreas.
3. Suppurative cholangitis.
4. Accidental operative injury of the common duct.
5. Idiopathic cyst of the common duct.
6. External compression of the common duct.

Of the 18 cases of choledochoduodenostomy reported by the author, the operation was followed by death in 2 cases. In 10 cases primary closure of the abdominal cavity was done. In 1 case a duodenal fistula occurred. In 4 cases, end-to-side anastomosis was done. The author states that the danger of backflow of intestinal contents into the common duct and, therefore, of ascending infection, is apparently less common when choledochoduodenostomy is done than when the gall-bladder is used in the anastomosis. In only one of the cases reported did postoperative x-ray examination reveal passage of the barium into the biliary passages. One female patient had attacks of cholangitis after the operation. The author leaves unanswered the question as to whether these symptoms were due to the operation or weakening of resistance.

**Results of Operative Treatment in Biliary Tract Disease.**—The results of *cholecystectomy* for well-defined cholecystic disease are, as a rule, highly satisfactory. J. F. Weir and A. M. Snell

(J. A. M. A. 105:1093 (Oct. 5) 1935) point out that the physician cannot expect 100 per cent. curative results from cholecystectomy alone when other visceral disease, systemic disorders and neuroses are present. Erroneous diagnoses and imperfect selection of cases are responsible for a majority of the cases in which postoperative symptoms appear. At operation an exacting technic and thorough examination of the common duct, liver and pancreas are essential. Recurring postoperative colic offers the greatest difficulty in diagnosis and treatment. This is most frequently attributable to stone in the common duct and to residual infection in ducts, liver and pancreas. In a few cases postoperative colic is not satisfactorily explained except on a neurogenic basis, and some type of biliary dyskinesia may be responsible for the difficulty.

The so-called *relapse* disturbances after operations on the gall-bladder, particularly after **cholecystectomy**, have convinced B. O. Pribram (München. med. Wchnschr. 82:1823 (Nov. 15) 1935) that there are disturbances which are manifestations of the abolition of the function of the gall-bladder. The recognition of the physiologic significance of the gall-bladder induced him to develop a conservative surgical method, *i. e.*, **cholecystocholedochostomy**. In this paper the author is chiefly concerned with the regulatory action exerted by the gall-bladder in the digestion of fat. He found that it contains a substance which is apparently secreted by the mural glands and which at a  $pH$  of 8.9 greatly intensified the action of the pancreatic lipase. The **mural extract of the gall-bladder** obtained by a surgical intervention exerts a much greater activator action on the pancreatic lipase than does the bile contained in the bladder. Chemical analysis of the substance disclosed that it is free

from protein and dialyzable. The author standardized the extract that contains the active substance, in that he designated as a unit the amount of activator substance which within 3 hours is capable of doubling the lipase action. The substance activates only lipases; it does not affect the action of proteolytic and saccharolytic ferments. In an oil digestion mixture it reduces the size of the droplets much more rapidly than does lipase alone. Following its parenteral injection there is an increase in the activator titer of the serum as well as of the duodenal juice. The quantity of bile increases likewise after the injection of the substance and it may therefore be concluded that it has also a choleric action. The author resorted to the therapeutic application of the substance in cases in which there were signs of abolished function of the gall-bladder and also in hepatic disturbances. The treatment resulted in the rapid disappearance of hepatic pressure and in a better tolerance for foods, particularly for those containing fat. Fat tolerance tests disclosed that the substance increased the resorption capacity for fats. Moreover, the substance proved helpful also in pancreatic disturbances, particularly diarrheas. In the therapeutic experiments the substance was usually administered by intramuscular injection (ampoules of 2 c.c.) and was always well tolerated; however, in the practical application it was given also in the form of tablets. Case histories indicate that the number of injections varied, some patients requiring only 1 or 2 and others 6 or more.

F. Bernhard (Deutsch Ztschr. f. Chir. 246:1 (Dec. 10) 1935) reports 1000 **choledochotomies** performed at the surgical clinic of the University of Giessen from 1895 to 1932. The numerical relationship between choledochotomies and cholecystectomies was as 1:



5. The mortality was 9.9 per cent. and was 3 times as great in men as in women. The most important cause of death was postoperative cardiovascular failure resulting from damage to the liver or pancreas. Peritonitis occupied a subordinate position as a cause of death. Icterus was present before the operation in 64 per cent., existed at some time in 17 per cent., and was absent in 19 per cent. The author considers icterus the most important indication for exploring the common duct. The common duct may be widened in the presence of a shrunken gall-bladder or from pressure by enlarged lymph nodes. Stones were not found in 6.9 per cent.; in 23.1 per cent. they were present in the biliary passages alone, in 11.6 per cent. in the gall-bladder only, and in 58.4 per cent. in both the common duct and the gall-bladder. The common duct was opened erroneously in 35 patients who had numerous small stones in the gall-bladder. The author considers this indication for choledochotomy overrated. Stones were found in the common duct when the gall-bladder was empty and shrunken. White bile was present in 22 cases and the mortality was twice the average. Stones were found in 15 of 38 patients who were submitted to a second choledochotomy. **Choledochoduodenostomy** is to be recommended for stricture of the lower end of the common duct and not as a primary operation for stones. An analysis of 180 deaths showed greater tendency to cholangitis in patients who have had several operations on the biliary tracts. Diabetes was more frequent after choledochotomies than after cholecystectomies. Liver cirrhosis developed later and with greater frequency in neglected cases. Cancer of the liver and the biliary tracts developed 15 years after the operation, on an average, in 20 patients. Of 687 patients followed

up, 389 recovered, 213 complained of mild symptoms, and 83 complained of more pronounced symptoms. In order to determine the causes of postoperative morbidity, the author made functional studies of the contents of the stomach, determinations of sugar tolerance, and determinations of the lipase and diastase content of the blood. Actual recurrence of stones was rare. Persistence of symptoms was due principally to cholangitis and liver damage, with an abnormal blood sugar curve. Chronic pancreatitis was present in more than 10 per cent. Subacidity and anacidity were found with particular frequency in the presence of pronounced complaints. In the treatment of *postoperative complaints*, the author stresses the value of **pepsin-hydrochloric acid** and of a remedy consisting of a preparation of **mercury, podophyllin, melissa, camphor and caraway**.

J. H. Saint (Brit. J. Surg. 23:299 (Oct.) 1935), in discussing late results of operation on the biliary tract, states that in both acute and chronic *cholecystitis*, with *cholelithiasis*, **cholecystectomy** was followed by better results than **cholecystostomy**. Excellent results were obtained in cases with and without choledocholithiasis in which **drainage of the common duct** was combined with **cholecystostomy** or **cholecystectomy**. Although several patients had 2 or 3 recurrent attacks after the operation, they ultimately became entirely well. Carcinoma of the gall-bladder did not develop in any case in which only cholecystostomy was done. The percentage of patients requiring a secondary operation was 5 times greater after cholecystostomy than after cholecystectomy. Cholecystographic studies made of 18 patients following cholecystotomy showed lack of impairment of gall-bladder function in 61 per cent. A

study of the preoperative history indicated that the patients with the shortest duration of biliary disease obtained the most relief from operation.

**INTESTINES.—MECKEL'S DIVERTICULUM.**—A study of histopathological findings and symptoms in cases of Meckel's diverticulum has been made by R. B. Greenblatt, E. R. Pund and R. H. Chaney (Am. J. Surg. 31:285 (Feb.) 1936)). Particular reference is given to heterotopic tissue and the classification of possible surgical complications.

In 9000 laparotomies, 18 cases of Meckel's diverticulum were found. The average age of the patient with such a diverticulum was 27 years. The ratio of females to males was 3.2. In 5 cases the diverticulum was symptomless and was found incidentally at operation for some other abdominal condition. In 6 cases inflammatory processes were present, and in 7 there was intestinal obstruction of varying degree. In 2 cases intussusception, and in 1 case volvulus, had occurred. In 1 case an umbilical fecal fistula was cured by excision of the diverticulum. Three cases showed heterotopic tissue.

Meckel's diverticulum should be looked for in all laparotomies, and the possibility of its presence should be considered in all cases of umbilical anomalies or vague paraumbilical pain, acute abdominal conditions, hemorrhage from the bowel, and intestinal obstruction.

During a period of 3 years, 4 cases of severe hemorrhage from the rectum due to a disease of Meckel's diverticulum were admitted to the Surgical Service of the Sheffield Royal Hospital. According to J. T. Chesterman (Brit. J. Surg. 23:267 (Oct.) 1935), 2 per cent. of all bodies contain Meckel's diverticulum. In 82½ per cent. of these the diverticulum lies free, in 10 per cent. it has a free or attached band at the apex, in

6 per cent. there is a fistula, and in the remaining 1½ per cent. there is some other abnormality.

*Hemorrhage* from Meckel's diverticulum may be due to a peptic ulcer of the diverticulum occurring at the junction of the aberrant gastric mucosa with that of the diverticulum. In rare instances it results from mechanical irritation when no aberrant mucosa is present. At times it is caused by inflammation, infarction, or neoplasm. About 85 per cent. of the cases are those of males. The hemorrhage is usually sudden and severe, but in cases of neoplasm it may be slight and continuous. Pain occurs in about half the cases. It is usually of the colicky type, but never severe or prolonged. About 25 per cent. of the subjects have nausea and vomiting unassociated with abdominal pain or obstruction. Examination is negative except for the finding of blood in the stool. Melena is rare between the ages of 5 and 15 years. Whenever it occurs, it should suggest the possibility of Meckel's diverticulum.

The *treatment* indicated for *massive hemorrhage* from the bowel associated with Meckel's diverticulum is **immediate operation for extirpation of the diverticulum**. If the hemoglobin is below 30 per cent., **transfusion** should precede the operation. In cases without perforation the prognosis is good.

*Congenital cysts and diverticula* (other than Meckel's diverticulum) and partial reduplications of the intestinal tract are unusual congenital anomalies. In the literature H. W. Hudson, Jr. (New England J. Med. 213:1123 (Dec. 5) 1935) has found records of 18 *reduplications or giant diverticula*. To these he adds 3 personally observed cases, one that of a male infant 3 months old, the second that of a female infant 6 months old, and the third that of a girl aged 12 years. In the first case the anomaly was

not recognized at operation and autopsy showed the condition to be of the jejunum duplex type, with the gastric mucosa presenting acute and chronic ulceration. In the third case the anomaly was recognized at once, probably because of the surgeon's experience in the first case. All of the patients died.

These cases add weight to the opinion expressed by the author in a report on Meckel's diverticulum that in the cases of infants and children with a long history of symptoms referable to the abdomen, a thorough exploration of the abdominal viscera should be made when other diagnostic methods prove inconclusive. This is important, especially if melena is a symptom. There is every reason to believe that **resection** of such anomalies is feasible and will relieve the symptoms if the laparotomy can be performed at a time when the patient is in good condition. As it is difficult to demonstrate these anomalies even at operation, Hudson suggests that transillumination of the mesentery may be helpful.

Anomalies of this type do not necessarily cause symptoms and in some instances have been incidental findings at the autopsy following death from an unrelated cause. Frequently, however, they are responsible for serious symptoms and death. The *symptoms* produced by those located within the abdomen may be broadly grouped as: (1) intermittent abdominal distress or pain, as in the author's second and third cases; (2) intestinal obstruction, as in the author's second and third cases; and (3) hemorrhage into the intestinal tract or peritoneal cavity or both, as in the author's first and third cases. These symptoms are readily understood, since obstruction, partial or complete, may be produced by encroachment of a cyst or diverticulum on the lumen of the intestine and by the production of volvulus and intus-

susception. Hemorrhage is best explained by the formation of ulcers in the mucosa adjacent to heterotopic gastric mucosa.

The vast majority of *acquired diverticula of the small intestine* are of mucous membrane hernia type similar to the pouches found in the large bowel. H. C. Edwards (Ann. Surg. 103:230 (Feb.) 1936) states that the first complete description of multiple jejunal diverticula was published by Sir Astley Cooper in 1844. The patient was a man 65 years of age. Since then, numerous cases of diverticula of the small bowel have been reported.

The author's material consisted of 6 postmortem and 3 operative specimens of acquired *diverticula of the jejunum and ileum*. Unlike duodenal diverticula, pouches lower down in the small intestine are difficult to detect by x-ray examination. In 7 of the cases reviewed by Edwards, from 1 to 18 diverticula were found in the jejunum. In 2 of those in which operation was performed, a solitary diverticulum was discovered in the jejunum, and in one, in the ileum and lower jejunum. Histological examination of 8 of the diverticula showed that they were all of the acquired type. In all but one instance the pouches arose from the mesenteric side of the small bowel. In one instance, a malignant growth was found associated with the pouch. The average age of the patients was 56 years.

Of a total of 12 cases from all sources, multiple diverticula were found in 5 and a single diverticulum was discovered in 7 instances. The site of herniation of the mucous membrane through the wall of the intestine corresponded to the site of entry of the blood vessels. In all but one case the diverticula were on the mesenteric aspect of the intestine. In large diverticula the fundus is completely devoid of a muscular coat. This is because the diverticulum increases in size

chiefly at the expense of the mucous membrane and submucosa, and eventually there is not sufficient muscular tissue in its wall to "go around." The diverticula discussed are acquired deformities of the bowel wall. The casual factors are the presence of a weakened area in the bowel wall, together with a pulsion force acting from within the bowel which initiates the process of herniation. The origin of jejunal diverticula corresponds exactly to the point of entry of the blood vessels through the muscular coat.

The two outstanding *symptoms* common to *diverticula of the jejunum* are: (1) vague abdominal pain occurring at an interval after meals, and (2) flatulence corresponding in time with the pain. It must be admitted that the symptoms of jejunal diverticulosis are not sufficiently characteristic to warrant a diagnosis of diverticulosis. X-ray examination is the final criterion. Rarely do jejunal diverticula give rise to clinical symptoms. When symptoms occur, the best treatment, whether a single diverticulum or multiple diverticula are present, is **resection** of the affected portion of the gut with **end-to-end** or **side-to-side anastomosis**.

**POLYPOSIS OF SMALL INTESTINE.**—H. Gatersleben (Deutsch Ztschr. f. Chir. 245: 628, 1935) reports the case of a girl who was subjected to laparotomy at the ages of 9, 17, and 20 years because of the symptoms of chronic ileus. The cause of the invagination found at the first operation, in which **resection of jejunum** was done, is not known. In the subsequent operations, the cause of the ileus was found to be an invagination produced by a polyp in the small intestine. The involved portion of bowel contained also several other polyps of various sizes. Although the polyps were removed after the small intestine was opened in the second operation,

another resection was necessary in the last operation. Since the third operation, the condition of the patient has been good. After the last resection no more polyps could be discovered in the rest of the small intestine or in the colon.

The author presents a review of the literature on polyposis of the small intestine. It has been found that polyposis of the small intestine is definitely an affliction of the young. Heredity plays a rôle in its development. The main clinical sign of the disease is invagination. Polyposis of the large intestine differs from polyposis of the small intestine in being generally disease of mature age and in its clinical picture, which is usually characterized by the appearance of blood and mucus in the stools. Polyposis of the small intestine is found more often in females than in males, while polyposis of the colon is more common in males.

On the basis of the studies of Schmieden and Westhues, the development of carcinoma from polyps of the colon has long been known. In the case reported by the author, histological studies demonstrated that carcinoma had developed from the polyps of the small intestine.

**TUBERCULOSIS OF INTESTINE.**—Thirty-two cases of tuberculosis of the small bowel are reported by H. R. Hartman (M. Clin. North America 19: 365 (Sept.) 1935). He states that the cases were classical according to symptoms. Usually, the intestinal lesion was associated with tuberculosis elsewhere, often with pulmonary tuberculosis. This series confirmed the observation that tuberculosis of the bowel is usually confined to the terminal part of the *ileum* and the proximal part of the *colon*. There were 7 cases of simple, non-specific ulcer of the small bowel. Operation was performed in 4 cases because of unexplained melena which in 3 cases

was associated with chronic anemia and in 1 case cramp-like abdominal pain. Of 3 patients who were operated on because of obstruction, 2 had complete obstruction of the bowel and 1 suffered from cramp-like pains, distention, and diarrhea characteristic of incomplete obstruction. Simple ulcers of the small bowel are rare.

In the *treatment* of intestinal tuberculosis, A. J. Rey, J. C. Rey, and A. Garcia de Loydi (Prensa méd. argent. 23: 1583 (July 1) 1936) report satisfactory results from **pneumoperitoneum** in 15 cases of intestinal tuberculosis secondary to pulmonary tuberculosis. The authors conclude that the technic of pneumoperitoneum is easy. It is advisable to perform the operation early in the development of intestinal tuberculosis, as soon as the complication is suspected. The operation is not contraindicated in patients in whom unilateral or bilateral pneumothorax has been previously performed. Pneumoperitoneum acts as a coadjuvant treatment to phrenicectomy by intensifying and strengthening the effects of phrenicectomy. Pneumoperitoneum results in rapid relief of diarrhea, pain, fever and the symptoms of gastric dyspepsia until complete disappearance. The patients regain a restful sleep and a feeling of euphoria. The satisfactory results of pneumoperitoneum as a symptomatic treatment are obvious. The value of the operation in producing complete recovery of the patients will be evaluated in time, after a more prolonged observation of the patients who, up to the present, can be considered as recently treated.

### INTESTINAL OBSTRUCTION.

—Since the beginning of the present century the operative *mortality* in cases of intestinal obstruction has remained steady at the high level of 40 per cent. Although in experiments on animals acute intestinal obstruction can be pro-

duced readily and its effects on the organism easily determined, the extensive knowledge gained from such experiments has not as yet been widely applied in treatment.

The relationship to clinical practice of certain recent experimental findings is discussed by I. Aird (Edinburgh M. J. 43: 375 (June) 1936). He classifies acute intestinal obstruction as follows:

*A.* Simple occlusion: (1) high obstruction of the small bowel; (2) low obstruction of the small bowel; (3) obstruction of the colon.

*B.* Closed loop obstruction: (1) loops with sterile contents; (2) loops with heavily infected contents; (3) loops with mildly infected contents.

*C.* Strangulation: (1) sudden anemia; (2) venous congestion; (3) short, long, and medium-sized loops.

*D.* Neurogenic obstruction: (1) spastic ileus; (2) adynamic paralytic ileus.

Wilkie, Haden and Orr, Draper-Maury, and many others have shown that in *simple occlusion* of the high type all of the phenomena are dependent upon the loss to the organism of water and inorganic ions which, poured into the stomach and duodenum in enormous quantities as digestive juice, fail to pass beyond the obstruction to be absorbed by the intestine below. The progressive loss of water leads to an increasing dehydration, the degree of which is indicated by dryness of the skin, increasing thirst, and a diminution of the urinary output. The blood becomes increasingly concentrated, the erythrocyte count and the hemoglobin rise, the viscosity of the blood increases, the sedimentation rate time becomes prolonged, and the total blood volume is reduced. The accompanying loss of the inorganic ions of the gastric, pancreatic, biliary, and duodenal juices lessens the electrolyte, chloride,

sodium, and potassium content of the blood. The body attempts to maintain the chloride level by complete retention of chlorides from the urine and the passage of chlorides from the tissues to the blood. The electrolyte content of the blood must be maintained and the lost chloride replaced. As the blood chlorides fall, the bicarbonate content rises and alkalemia results. Coincident and parallel with the fall in the blood chlorides is a rise in the nonprotein nitrogen and urea of the blood.

All of these phenomena—dehydration, hypochloremia, and alkalemia—therefore depend primarily upon the loss of water and sodium chloride from the digestive juices. The most rapidly fatal form of simple occlusion results when the obstruction is located just below the entrance of the biliary and pancreatic ducts—the “lethal line” of Draper-Maurey.

The *treatment* of duodenojejunal occlusion is the well-known **gastric lavage** and the **intravenous** administration of **saline solution** followed by **removal of the obstruction** or a **short-circuiting operation** after the dehydration and hyperchloremia have been relieved. Hypertonic saline solutions have no place in the treatment of high occlusion. Only physiological saline solution should be administered. Hypertonic saline solution may even be harmful. The quantities of saline solution usually given are inadequate. A patient suffering from high obstruction may lose 8 liters (quarts) of fluid in 24 hours. The saline solution should be given intravenously until the blood-chloride level approaches the normal. A safe procedure consists in **washing out the stomach** and giving 2 liters (quarts) of **saline solution intravenously** and slowly. Dehydration is manifested by a parched condition of the tongue, dryness of the skin, and concentration of

the urine. If a drop of silver nitrate solution is added to acidulated urine, the appearance of a white precipitate indicates the presence of chlorides. If the urine contains chlorides, the blood chloride is sufficiently high for operation to be performed safely.

In *occlusion of the lower ileum*—the common clinical form of obstruction of the small bowel—vomiting is a late feature. The digestive juices continue to be absorbed until late in the course of the condition. Even in the later stages, dehydration is relatively slight and the maximum loss of blood chlorides is only 30 per cent. Therefore, there is no great change in the alkali reserve and no great elevation in the nonprotein nitrogen.

Formerly the theory that death from intestinal obstruction was due to bacterial toxins was widely accepted. It is now agreed quite generally that no bacteremia occurs in intestinal obstruction in man.

Sudden relief of intestinal obstruction is followed by a rise in the blood-pressure. Sudden release of a long-continued distention of the bowel with severe cyanosis is likely to be followed by a dangerous fall in the blood-pressure. The surgeon should hesitate, therefore, to drain a grossly distended bowel suddenly. Wangensteen's suggestion of **pre-operative nasal drainage** appears excellent, as this procedure would prevent sudden flooding of the general circulation by depressor blood from the recovering bowel. Wide excisions of bowel seem inadvisable under any conditions. No loop of bowel should be excised unless it has obviously lost its vitality. A doubtful loop should usually be left.

In the majority of clinical cases, simple occlusion of the colon is the result of carcinoma. Since it becomes acute only after the tumor has been present several months, the changes of acute obstruction become superimposed upon those of the chronic type. Before the

obstruction becomes complete, the bowel is already dilated, its muscle walls are hypertrophied, and the mucosal wall is not infrequently the site of stercoral ulceration. The patient is often cachectic and in poor general condition. As a result of the obstruction, the intracolonic pressure may reach a high level. Perforation of the colonic wall may occur through a stercoral ulcer, with consequent fatal peritonitis.

In the experimental animal, *colonic occlusion* is the most slowly fatal of all forms of acute intestinal obstruction. An animal with complete occlusion may live untreated for as long as 30 days. There is no significant change in the blood chlorides. The blood urea and non-protein nitrogen are only slightly elevated. The treatment suggested for the condition is **drainage by gradual decompression of the bowel**.

Wilkie demonstrated that in *closed-loop obstruction of the bowel* the pathological course depends upon the degree to which the contents of the loop are infected. If the contents of a doubly obstructed loop are sterile, the loop merely distends slowly as a mucocele. The best example of such a condition is *mucoceles of the appendix*. The best clinical example of obstruction of a loop with heavily infected contents is *obstructive gangrenous appendicitis*. Such a loop contains grossly infected fecal material. The organisms multiply rapidly, gas accumulates in the lumen, the intraloop pressure increases rapidly, fluid and leukocytes are poured into the lumen, and a pyocele forms rapidly. The increasing pressure interferes with local circulation, organisms enter the devitalized bowel wall, and gangrene, perforation, and peritonitis result.

The author's scheme of *treatment* for the various forms of intestinal obstruction is as follows:

Simple occlusion in high obstruction of the small bowel: the administration of **physiological saline solution** until chlorides appear in the urine, followed by **operative relief of the obstruction**.

Low obstruction of the small bowel in which chlorides are absent from the urine: the **intravenous** administration of **saline solution** until chlorides reappear in the urine.

Obstruction associated with marked venous congestion: **gradual decompression**.

Colonic obstruction: **gradual deflation of the bowel**.

Closed sterile loop obstruction: **resection of the loop**.

Obstruction of a loop with heavily infected contents: **resection**.

Obstruction of a loop with mildly infected contents: the **treatment for low bowel obstruction**.

Long-loop obstruction: **blood transfusion** followed by the **treatment given for obstruction of a loop of medium length**.

Obstruction of a loop of medium length: **blood transfusion** and **removal of the toxic transudate from the peritoneal cavity** followed by **resection or exteriorization of the involved loop**.

In clinical intestinal obstruction, injury to the bowel is due chiefly to distention and venous obstruction. W. D. Gatch and C. G. Culbertson (Ann. Surg. 102: 619 (Oct.) 1935) point out that *distention* causes a decrease in the blood flow through the bowel wall which is in direct proportion to the elevation of the pressure. When it reaches the level of the diastolic blood-pressure, it almost stops the flow of blood. At this level it stops all absorption by way of the mesentery. Transperitoneal absorption then occurs. Distention sufficient to arrest the circulation of the bowel will devitalize the intestinal

mucosa in from 5 to 15 hours. The devitalization is evidenced by the loss of selective absorption by the mucosa. It then permits the passage of toxic substances present in the normal obstructed bowel. The absorption of materials normally absorbable by the bowel, except water and probably inert gases, proceeds at a relatively uniform rate in the presence of intrainestinal pressures between zero and the diastolic blood-pressure. Final conclusions regarding the effect of distention on the absorption of water and inert gases have not been made.

*Venous obstruction* subjects the capillaries of the bowel to the full force of the systolic blood-pressure. This accounts for the rapid destruction of the bowel wall. The circulation of the obstructed bowel is not greatly influenced by the increased intraabdominal pressure which accompanies intestinal obstruction. The blood flow through distended loops of intestine must be lessened by any weakness of the systemic circulation.

Toxic material present in the lumen or wall of the obstructed bowel may reach the systemic circulation by way of: (1) the mesenteric vessels, or (2) the peritoneal cavity. Before the passage of any toxins which the authors can imagine to be present by either route or under any conditions can occur, injury to the mucosa must exist. Injury observed under clinical conditions to the mucosa of the obstructed bowel is due practically to two causes only: (1) distention, and (2) venous congestion. Any passage of toxins from a bowel with devitalized mucosa must be transperitoneal as long as its circulation is stopped by pressure or obstruction; by way of the mesentery if its circulation is present. The body is protected in a fairly adequate manner from absorption of toxins by way of the peritoneum. The sudden relief of obstruction in the

presence of devitalized mucosa may permit the rapid absorption of toxic substances by way of the mesentery.

In the clinical management of patients suffering from advanced obstruction, it seems desirable to **deflate the bowel gradually before operative relief** of the obstruction is undertaken. Otherwise the barriers against absorption of the toxins by way of the peritoneum and against their rapid absorption by way of the mesentery may be broken down.

*Varieties.*—R. Miller and H. C. Gage (Lancet 2: 115 (July 20) 1935) discuss *chronic duodenal ileus due to arterio-mesenteric compression* as a cause of symptoms in early life. They believe that the gastric symptoms are due to congenital anatomical compression and gastric distention, and that gastric distention is the cause of the more urgent symptoms of obstruction even in the cases of newborn infants. The vomiting of bile is exceptional. The children are frail and underweight. The chief symptoms are a persistent lack of appetite and periodical attacks of vomiting. A rather characteristic symptom is hiccup. There is a tendency toward diarrhea rather than constipation. The most characteristic physical sign is protuberance of the upper part of the abdomen due to the enlargement and hypertrophy of the stomach. X-ray examination serves to distinguish between complete and incomplete duodenal obstruction and excludes the pylorus as the site of the obstruction. For the best results from x-ray examination the opaque meal must be considerably larger than that usually employed for children of the same age, and marked gastric dilatation must be relieved before the examination is undertaken.

In discussing the cases of *newborn infants* the authors state that absence of bile in the vomitus does not exclude the presence of chronic duodenal ileus,



and the persistent presence of an excess of mucus in the vomitus in a case of chronic vomiting signifies obstruction at the pylorus or in the duodenum. In the x-ray examination the opaque meal should be large and given immediately after the stomach has been thoroughly washed out. Serious vomiting can be stopped by **gastric lavage**. For this purpose the authors use a dilute **solution of sodium bicarbonate**. They state that gastric lavage should be done at first every 12 hours, but when the washings have become clearer, the intervals may be increased to 24, 36, and 48 hours. Thereafter, lavage should be done every 2 or 3 days for about 3 months.

In *late infancy and early childhood*, constant hiccup, enlargement and protrusion of the stomach, visible peristalsis, and a persisting splashing suggest stasis and obstruction. These conditions can be demonstrated by x-ray examination with an opaque meal. In the treatment of the ileus it is essential to separate ingested fluids from solid food as much as possible and the meals should be well spaced apart. A mixed diet slightly low in fat should be given. The food should be minced and as dry as is palatable. **Fluids** should be given about 3 hours after meals. In the early stages a mixture containing  $\frac{1}{2}$  dram (2 Gm.) of **glycothymolin, rhubarb, and soda** is of great value. Later, **hydrochloric acid drinks** may be allowed with meals. The use of paraffin as an aperient should be avoided. **Massage** and **ultraviolet light** may be helpful. **Exercise** and **fresh air** are beneficial. As a rule, operation is not advisable. The *prognosis* is good.

*Spastic ileus* in a man, aged 23, is reported by K. Boman (Hygiea, Stockholm, 98:465 (July 31) 1936). The patient had a wound infection of one foot but no gastric disorder and was in

good general condition, when a disturbance with a picture of high ileus set in and resisted conservative treatment. On operation, the upper loop of the jejunum showed a sharp transition between a proximal dilated, reddened intestinal portion, including duodenum and stomach, and a distal pale and collapsed portion. At the place of transition a round anemic edematous efflorescence appeared, followed by a contraction ring, which obstructed the lumen; on palpation, this disappeared, to be followed by another spasm in the same manner. The spasm is ascribed to a circulatory disturbance, and the circulatory disturbance in the intestine is regarded as a partial phenomenon of a general circulatory disorder expressed by the shock-like condition of the patient at the onset. This disturbance is attributed to intoxication from the wound with its breaking-down products. A doubly fenestrated soft catheter was introduced in the stomach for drainage. Attempts to improve the circulation by administration of fluids and other means, and use of spasmolytics and other preparations to restore intestinal tonus through the vegetative system were without effect. On the sixteenth day the patient died in a new attack with collapse, falling temperature, pain and hiccups, together with marked aggravation of the general condition, small pulse and tachycardia. Necropsy failed to reveal any mechanical cause of the ileus or other positive results.

*Acute mechanical obstruction of the bowel* by a *gall-stone* is a well-recognized though uncommon entity. Most of the gall-stones gaining entrance to the intestinal tract are voided naturally. Stones sufficiently large to cause bowel obstruction never pass the entire length of the bile duct, but enter the bowel by a process of ulceration. Such stones are usually more than 1 inch in diameter.

Because of the large number of symptomless cases of gall-stones, obstruction of the bowel by impacted gall-stones is not likely to become infrequent. In such cases there is always the possibility of symptomless ulceration with subsequent obstruction. After causing obstruction, a gall-stone may become free and be voided naturally.

C. P. G. Wakely and F. W. Willway (Brit. J. Surg. 23:377 (Oct.) 1935) review 11 cases of intestinal obstruction by *gall-stones* in which operation was performed. The ages of the patients ranged from 44 to 81 years and averaged 66 years. All of the patients were women. There were 3 deaths, a mortality of 27 per cent. Not infrequently operation was delayed because the obstruction tended to be intermittent. Four of the patients gave a definite gall-bladder history. The others complained of dyspepsia, indigestion, or other vague symptoms. A preoperative diagnosis of intestinal obstruction due to a gall-bladder stone was made in only 2 cases. In all of the cases a stone was impacted in the small bowel. One patient had a second stone impacted in the rectum. Six patients had a cystoduodenal ulceration, and one, an ulceration of the common duct. In the others it was impossible to be certain which form of fistula was present.

With regard to the mode of production of *biliary fistulæ*, the authors state that the gall-bladder seems to have a natural tendency to become adherent to adjacent structures. Gall-stones favor fistula formation by causing pressure necrosis of the gall-bladder wall. *Fistulæ* so produced open most frequently into the duodenum or colon. After the stones have been successfully extruded into the bowel, contraction of the fistula begins. This is followed by shriveling of the gall-bladder. The projecting gall-stone may be lodged in the lumen of

the intestine for some time before it becomes dislodged. Specimens showing the different types of biliary fistula are described.

*Ileus* associated with *strongyloides infestation* is described by J. O. Nolasco and C. M. Africa (J. Philippine Islands M. A. 16:275 (May) 1936). The authors report a fatal case of intestinal obstruction due to paralytic ileus associated with a severe infestation with *Strongyloides stercoralis*. The discovery of filariform larvæ in the muscular and serous coats of the jejunum, ileum, appendix, large intestine and liver tends to confirm the theory advanced by Gage, Ophuls and Nishigori that reinfection in strongyloidosis can take place in the intestine. Traumatism was evident and was shown by marked congestion and swelling of the mucosa of the small intestine and the formation of small submucous abscesses in the large intestine. The vomiting and abdominal distention and tenderness with tympanism before death and the postmortem observations of intestinal obstruction without any apparent gross organic cause can be explained only by a massive invasion of the intestinal wall. The weak condition of the patient and the stasis of the intestinal contents possibly induced a larger number of the infective forms to penetrate the intestinal wall. That there was an overwhelming extensive infestation was also shown by the abundant larvæ found in the feces at necropsy. That the presence of the larvæ in the deeper layers of the intestinal wall and liver was not due to postmortem migration is indicated by the presence of inflammatory changes, such as tubercle formation around the larvæ. In spite of the usual absence of alarming symptoms, strongyloidosis must be regarded as a serious disease. The patient's infestations had been observed since admission to this colony in June, 1930. His death

could not be attributed to any cause other than the heavy infestation with *Strongyloides*.

**INTUSSUSCEPTION.**—Thirty-five cases of intussusception have been studied by H. Fuss and L. Leurs (*Beitr. z. klin. Chir.* 161:117, 1935). Of the cases reviewed, 74.3 per cent. were males and 62.9 per cent. were in the first or second year of life. In the infants the condition was most frequent at about the middle of the first year and no anatomical cause for the intussusception could be found. In cases in which the invagination occurred after the second decade of life, polyps, connective tissue bands, and Meckel's diverticulum were discovered. In 2 cases the exciting cause was trauma due to heavy lifting. In 14 of 19 infants and 5 of 9 adults the invagination occurred at the junction of the small bowel with the cecum. In 18 of the 19 cases of invagination in infants, vomiting occurred and the feces contained blood, and in 10 of these 18 cases there was a palpable tumor. Palpation was often made difficult by the prognostically unfavorable meteorism.

In the cases of the 9 patients in the second decade of life or older, it frequently led to an incorrect diagnosis. The most common **erroneous diagnoses** were stenosis of the bowel, ileocecal tumor, and ileus.

Since the work of Anschuetz, the conservative *treatment* recommended by Danish surgeons has been abandoned and **early operation** has been performed. In all of the 19 cases of invagination in *infants* operation was performed immediately. The earlier the operation, the lower the mortality. The dividing line between safety and danger is about the twenty-fourth hour. In the cases of infants, a chance for a successful result is offered, as a rule, only by **disinvagination**. Resection is practic-

ally never successful. Anschuetz reported 3 deaths in 17 cases in which disinvagination was done and 8 deaths in 9 cases treated by resection. After the twenty-fourth hour disinvagination is rarely possible and the chance for a successful result decreases rapidly.

In cases in which the condition occurs after the second decade of life the *prognosis* is considerably more favorable even when operation is performed late, the mortality being only 33.4 per cent. This is probably explained by the usually more chronic course of the condition at this age and the fact that older children and adults tolerate resection much better than young children.

Commenting on *irreducible intussusception*, A. Elliot-Smith (*Lancet* 2:992 (Nov. 2) 1935) believes that the most important factor in making an intussusception irreducible is delay in its relief. Vascular obstruction leads to congestion, edema and finally gangrene of the intussusceptum, while at the same time peritoneal adhesions are forming between the entering and returning layers. The correct *diagnosis*, in a typical case, depends on the history of acute abdominal pain, vomiting, presence of a tumor, and usually the passage of blood by rectum. In 3 of the author's cases a diagnosis was not made until blood was passed rectally, with the result that operation was delayed. In the common ileocecal intussusception of infants, the small intestine passes rapidly into the colon and may even appear at the anus within a few hours. Severe symptoms and all the typical signs are frequently present within a short time of the commencement of the illness. At early operation **reduction** is usually easy and the distance the intussusception has traveled does not necessarily increase the gravity of the prognosis. Intussusception commencing in the small intestine advances less rapidly than the ileo-

cecal type, because the entering and ensheathing layers are of much the same lumen and the symptoms are much less severe, so that diagnosis is more difficult. The ensheathing layer forms a tight constriction at the neck of the intussusception, which makes reduction difficult. In these cases indefinite symptoms and the tight constriction at the neck of the base both favor the production of an irreducible intussusception. The 4 cases reported were all of this last type; one had remained entirely enteric, while the other three had reached the colon by passing through the ileocecal valve. The patients were children aged 2 years and 4 months, 7, 10 and 11 years, respectively, who are better able to stand abdominal operations, but the treatment suggested (**lateral anastomosis**) is applicable to cases of irreducible intussusception in *infants* and probably offers a better chance of recovery than resection. Lateral anastomosis relieves the obstruction and largely avoids the shock and dehydration associated with resection and ileostomy. Lateral anastomosis to short circuit the obstruction offers the best chance of recovery.

An observation has been made by E. Ehnmark (Acta chir. Scandinav. 76: 147, 1935) that in the case of *cecal tumor associated with intussusception*, x-ray examination be made during an attack of pain. At other times the intussusception is easily reduced and therefore may escape *diagnosis*. The author discusses cecal tumor with intussusception, commenting on 132 cases in the literature and an additional 7 cases from the University of Upsala.

**Treatment.**—M. M. Miller and C. L. Beatty (Ohio State M. J. 31:759 (Oct.) 1935) state that the possibility of avoiding operation in certain selected, promptly diagnosed cases of intussusception has not been sufficiently recog-

nized. The desirability of an effective means of relieving intussusception without repeated resort to surgery is especially great in the case of individuals with recurrent attacks. They believe that it is in such cases that the non-surgical approach of Retan and Stephens may be of the greatest value. In their case of *recurrent acute intussusception*, the child had one attack at the age of 20 months and a second attack nearly 3 months later. In both attacks the child presented the symptoms (sudden onset, intermittent abdominal cramps, prostration and collapse) and the characteristic sausage-shaped tumor mass of intussusception. In neither attack had sufficient time elapsed for the passage of mucus and blood. In both attacks the diagnosis of intussusception was confirmed by a barium sulphate fluoroscopic examination within 3 hours of the onset and the obstruction was relieved by extraabdominal manipulation. The use of **barium sulphate enemas** and **massage under the fluoroscope** appears to be a valuable procedure deserving a therapeutic trial in all very early cases of acute intussusception.

The *rôle of the ileocecal sphincter* in cases of obstruction of the large bowel is outlined by L. Sperling (Arch. Surg. 33:22 (Jan.) 1936). The author has shown that the ileocecal sphincter is able to withstand moderate increases of intraenteric pressure such as occur in obstruction of the colon. In clinical cases of such obstruction the intraenteric pressure has been found to vary from 10 to 50 cm. of water.

A competent ileocecal sphincter prevents regurgitation into the ileum and converts what would otherwise be a simple type of obstruction into a closed loop, with all the inherent danger of strangulation due to increasing intraenteric pressure. In experiments on dogs, pressures of from 30 to 50 cm.

of water maintained for 24 hours produced areas of hemorrhagic necrosis in the colon. That similar changes take place in the human colon is evident from a perusal of the literature and the cases reported by the author.

The term "*ileocecal valve*" is a misnomer. The organ is more rightly called the "*ileocecal sphincter*." It is subject to definite nervous control, and its competency depends on the tonicity of its fibers. That the tone of the sphincter is increased by stimulation of the sympathetic nerves is confirmed by the author's experiments. It has been shown also that stimulation of the distal part of the colon increases the resistance of the sphincter to backpressure to approximately 3 times that of the normal sphincter. Stimulation of the parietal peritoneum, the stomach, or the small bowel has no such effect. It is conceivable that the resistance of the ileocecal sphincter to backpressure is greatly increased in cases of intrinsic pathological conditions of the colon. Stimulation of the distal portion of the colon, acting through Auerbach's plexus, increases the tone of the ileocecal sphincter, making it more competent.

The author cites the following important clinical observations with relation to a competent ileocecal sphincter in cases of obstruction of the large bowel:

1. Vomiting is a late symptom in obstruction of the large bowel. The competent ileocecal valve allows material to pass into the colon but none to be regurgitated into the small bowel and stomach. In the cases cited, aspiration of the stomach resulted in the return of only a few cubic centimeters, in spite of the fact that these cases represented late stage of obstruction.

2. Nasal suction as a method of decompression is of little value in the treatment of acute obstruction of the large bowel with considerable distention.

3. A single roentgenogram of the abdomen of a patient with clinical intestinal obstruction should differentiate between obstruction of the small bowel and of the large bowel. The x-ray demonstration of marked distention of the colon and dilatation of the cecum with no visible loops of small bowel should clinch the diagnosis of obstruction of the left colon.

4. All *acute obstructions of the large bowel* exhibiting considerable *distention* should be treated as obstructions of the closed-loop type with potential strangulation, by means of operative decompression (*cecostomy* or *transverse colostomy*).

**Cause of Death.**—The observations on more than 250 necroptically corroborated cases of intestinal occlusion by F. Starlinger and R. Scholl (Wien. klin. Wchnschr. 48:1232 (Oct. 11) 1935) indicate that *peritonitis* is the cause of most fatalities in intestinal occlusion, *pneumonia* and *circulatory failure* being the other chief causes. In the last analysis, even the fatal outcome of peritonitis is really a circulatory collapse. They show that uncomplicated intestinal occlusion, which as yet has caused neither peritonitis nor destruction of the intestinal wall, is accompanied by a severe disturbance in the intermediate and sodium chloride metabolisms, which, in turn, are partly the result of a severe hepatic impairment and lead to severe dehydration of the tissues. Thus, there develops an inspissation of the blood, a capillary stasis, a continuous decrease in the amount of the circulating blood and a failure of the so-called venopressor mechanism, which plays an important part in the maintenance of the circulation.

Following a description of observations on dogs, Starlinger and Scholl (*Ibid.*) conclude that the failure of the circulation is the chief cause of death

in intestinal occlusion. In accordance with this knowledge, they advise **early surgical treatment**, which should aim at the smallest possible intervention. Moreover, attempts should be made to counteract the metabolic disturbances, to promote the hepatic function and to support the circulation. They advise that **sodium chloride** be administered in the form of **hypertonic solutions**, 5 per cent. **solutions of dextrose**, together with small quantities of **insulin** and **blood transfusions**. If *peritonitis* has already developed, **peritonitis serum** should be administered. To stimulate diaphragmatic respiration and the circulation, **carbon dioxide** should be given in carefully adjusted doses. As soon as the intestinal obstruction has been counteracted, **peristalsis** should be **stimulated**.

According to V. H. Moon and D. R. Morgan (Arch. Surg. 32:776 (May) 1936), there is much evidence that in intestinal obstruction death is due to circulatory failure of the *shock* type and the physiological disturbances are those usually seen in the shock syndrome.

The gross and microscopic visceral changes are identical with those accompanying shock produced by various means. Injury to the capillaries is evidenced by capillary hemorrhages, the formation of edema fluid with a high protein content, and the rapidity with which colloidal dyes escape from the blood into the tissues.

The probable cause of the shock syndrome following intestinal obstruction is intoxication by histamin, other products of injured tissue, and bacteria and their products absorbed from the obstructed bowel.

**POSTOPERATIVE INTESTINAL OBSTRUCTION.**—E. Pescarmona (Policlinico (sez. prat.) 42: 1889 (Sept. 30) 1935) advises the use of dimethyl carbamic ester of oxyphenyl-

trimethyl-ammonium methyl sulphate (**prostigmine**) injections in the amount of 1 c.c. (16 minims) of a .05 per 1000 isotonic stable solution at each injection, *i. e.*, 0.0005 Gm. ( $\frac{1}{120}$  grain) of the active substance in 1 c.c. (16 minims) of the solution, in the treatment of post-operative dynamic intestinal obstruction. This treatment gives satisfactory results even in cases in which the ordinary methods of treatment, such as enemas, the use of a rectal sound, intravenous injections of hypertonic salt solution and hot cataplasms, have failed. It does not produce harmful effects on the heart or on the arterial pressure, or clinical complications of any sort. The abdominal pain with which some patients react is transient and tolerable. As a rule, one injection of the mentioned dose is sufficient to obtain satisfactory results. Nevertheless, in severe cases two or more injections (up to 5 or 6) may be given at intervals of a few hours during the same day without any danger to the patient and usually with good results. Although the injections may be given either intravenously or intramuscularly, the latter technic is preferable because of its simplicity.

K. Schlaepfer (West. J. Surg. 44: 437 (July) 1936) confirms the experiences of other observers with the use of **prostigmine** and claims that he was dealing with an excellent peristaltic agent—one without undesirable by-effects. For injections, he always uses the intramuscular route. He gives the first injection from 8 to 10 hours after laparotomy. However, in cases in which he expects considerable stasis as a result of prolonged exposure of the open abdominal cavity and handling of the intestine, he feels justified in shortening the interval before the first injection. The second injection is usually given after an 8-hour interval. About 15 to 20 minutes after the injection, increased

peristalsis becomes noticeable by expulsion of flatus. The great majority of the author's patients did not complain of cramps. Half an hour after the injection, a **glycerin-water enema** (100 c.c.) is given. This usually is followed by a copious evacuation. He used and is using the physostigmine derivative as a *preventive measure against atony following major abdominal operations*, when other measures, such as the light arc or electric pad in conjunction with enemas, would probably not suffice. Cases of acute abdominal conditions necessitating immediate surgery, such as appendicitis, perforated gastric or duodenal ulcer, or cholecystitis, are greatly benefited by the early and persistent post-operative use of the physostigmine derivative until normal peristalsis is reestablished. Following *operations for hemorrhoids, anal fistula and fissures* in which the peristalsis is checked for several days by opiates, it proves valuable in starting peristalsis. In *paralytic ileus due to peritonitis*, it is helpful in promoting and sustaining effective peristalsis. A change in technic, which proved superior to the original procedure, was the replacement of the glycerin-water enema by a slowly given **enema** of 100 c.c. (3½ ounces of 15 per cent. **solution of sodium chloride**).

G. Loewe and J. Herbrand (Beitr. z. klin. Chir. 162:201 (Sept. 14) 1935) show that *intestinal peristalsis* is regulated by nervous and hormone actions. In discussing the treatment they point out that the great number of suggested remedies indicates the absence of an entirely satisfactory one. In view of this fact, they resorted to treatment with a **posterior pituitary preparation** that influences the vascular system and the intestine. They report a number of cases in which they used this preparation with good success. Strictly individualized dosage stimulated the peri-

stalsis and the intestinal evacuation even in the most severe cases of intestinal atony without causing circulatory disturbances or impairing the general condition. The clinical observations on the efficacy of the pituitary preparation were corroborated by x-ray studies. In serial x-ray examinations it was observed that a few minutes after the injection of smallest amounts the peristalsis increased and reached its maximum after from 10 to 15 minutes. The authors reach the conclusion that this posterior pituitary preparation is an excellent remedy for the stimulation of the disturbed peristalsis.

**MORPHINE AND INTESTINAL ACTIVITY.**—Intubation studies of the human small intestine relating to the *motor effects* of single clinical doses of *morphine sulphate* in normal subjects have been made by W. O. Abbott and E. P. Pendergrass (Am. J. Roentgenol. 35:289 (Mar.) 1936). By means of intrainestinal balloon studies, combined balloon and x-ray studies, and x-ray studies after a barium meal, the authors found that the effect of a single clinical dose of morphine on the human small intestine is stimulating. The increased tonus is greatest in the most reactive region of the bowel, the duodenum, and is slight or absent in the ileum. During the period of increased tonus the height of the contractions is diminished in proportion to the degree to which the increased tonus prevents "diastole," and there is the usual increase in the rate proportional to the reduction in the amplitude. Twenty minutes later a depressant action, which may last for hours, sets in, the tonus falling in the sense of lengthening of the muscle fiber. This secondary effect occurs to a far greater degree in the duodenum than in the ileum. Contractions increase in amplitude for a brief period as the

falling tonus reaches the optimum level for their occurrence, and subsequently diminish roughly in proportion to the degree of fall in the tonus.

The general effect of these changes is first to make the gradient of tonus steeper, causing an initial rapid downward flow of duodenal and high jejunal contents toward the ileum, and then to level off the gradient, leading to marked prolongation in the emptying time of the intestine. From the broad standpoint it may be construed as further evidence that small intestinal motility is related primarily to tonus differences rather than to contraction waves, since the effectiveness of the waves seems to depend primarily upon the tonus level from which the waves arise.

The authors believe that these findings are unfavorable to the use of morphine in conditions associated with intestinal distention unless the other advantages of the drug outweigh this aspect of its action. They prefer to withhold final judgment until the effect of repeated doses of the drug has been studied.

Morphine was formerly believed to be a "bowel splint" because of its supposed immobilizing effect on the intestine. It is now thought that in the ordinary dosage of  $\frac{1}{8}$  and  $\frac{1}{4}$  grain (8 and 16 mg.) it produces its beneficial effects by stimulating motility and tone.

F. F. Yonkman, J. M. Hiebert and H. Singh (New England J. Med. 214: 507 (Mar. 12) 1936) studied the effects of morphine in the cases of 5 patients, a woman and 4 men. Two of these patients had a Mikulicz operation, 1 a cecostomy, and 2 a colostomy. A graphic record of the bowel activity was obtained by the method of Plant and Miller. In this procedure long, sausage-shaped balloons of rubber tied to rubber catheters are introduced into the lumen

of the large and small intestines. The catheter is connected to a water manometer in which any change in water level and air volume is recorded graphically on a smoked paper on the kymograph through a modified Brodie air bellows. The kymograph is so placed at the bedside that the patient is unable to see the record.

All of the patients studied by the authors showed some form of stimulation of either the ileum or the colon, the result depending on the individual patient, the dosage of morphine, and the bowel area studied.

In cases of suspected *peritonitis* morphine should be employed to prevent excessive bowel distention, the dosage being repeated at intervals of 3 or 4 hours. When there is danger of perforation of a weakened bowel, an increase in tone produced by morphine may be advantageous. It is possible that *postoperatively*, by increasing the bowel tone, morphine may relieve the so-called "*gas pains*" by preventing distention. Increased bowel activity promotes the passage of gas and improves its absorption as well as the absorption of liquids. It appears that the comfort produced by morphine is due to a peripheral stimulating action in the intestine as well as a central depressant action on pain perception. In *intestinal hemorrhage*, **morphine** will give relief more quickly if the tonus is increased.

Recent studies by J. Fine, B. M. Banks, J. B. Sears and L. Hermanson (Ann. Surg. 103:375 (Mar.) 1936) on animals demonstrated that nitrogen and hydrogen are the major constituents of the gases causing distention, and that the inhalation of pure **oxygen** effects a substantial reduction in the gas volume of the obstructed small intestine inflated with these gases. The inhalation of pure oxygen accomplishes this result by preventing the entrance of atmospheric



nitrogen into the lungs. As the result of this action, the nitrogen in the blood and tissues is rapidly exhaled at the rate of 60 per cent. per hour. The consequent fall in the partial pressure of this gas in the blood not only prevents its diffusion from the blood into the intestine, but accelerates its diffusion from the intestine into the blood. Experiments showed that after the inhalation of pure oxygen for 24 hours the volume of nitrogen originally injected into the small intestine obstructed at the pylorus and the ileocecal valve was reduced approximately 62 per cent. in comparison with an absorption of about 10 per cent. when air is breathed. It was found that the decompressing action of oxygen is ineffective for the distended stomach, its usefulness being primarily restricted to the small intestine.

The oxygen tents in current use do not provide a concentration higher than 70 per cent. The authors describe their **modified Barach tent** which will yield an oxygen concentration of 95 per cent. for the treatment of *obstinate distention*. To date, they have used this tent in the treatment of 5 patients. That this mechanism operates effectively in man was apparent from the considerable decrease in the girth of the abdomen observed after inhalation of the 95 per cent. oxygen for periods of from 8 to 24 hours and before any gas was passed by rectum. None of the patients were victims of mechanical obstruction, and all of them eventually completed the deflation spontaneously. The fact that under all of the usual methods for the treatment of distention they failed to expel the gas for several days preceding the administration of oxygen, suggests that the oxygen permitted the unobstructed but overdistended bowel to recover effective peristaltic activity simply by causing partial shrinkage of the bowel lumen. It cannot be denied, however, that the deflation

attributed to the oxygen might have occurred without its use. Because of its toxic properties, the 95 per cent. oxygen mixture must be administered intermittently.

In conclusion, the authors state that while the results in their 5 cases do not conclusively demonstrate the value of the described treatment, they are sufficiently gratifying to justify further trial of the method.

**DUODENUM.—Radiography.**—It is claimed that in examination of the duodenum modern roentgenography is more exact and more reliable than either clinical or laboratory investigation. Provided an appropriate technic is employed, there is no other portion of the alimentary tract which can be so thoroughly investigated as the duodenal cap. By the "aimed exposure with dosed compression" developed by Berg or Hamburg, the x-ray diagnosis of *duodenal ulcer* can be made with almost mathematical accuracy, as in the majority of cases the inner aspect of the cap is shown as clearly in the roentgenogram as in the resected specimen. G. R. M. Cordiner and G. T. Calthrop (Brit. J. Surg. 23: 700 (Apr.) 1936) claim that in this procedure various degrees of compression are applied to allow presentation of the mucosal relief, and aimed exposures are taken at various angles and positions. In cases of *duodenitis* the mucosal relief shows changes analogous to those found in hypertrophic gastritis. The folds are broadened, as are the intervening hollows, and appear to have lost their elasticity, being less easily deformed by pressure. Because of their depth, pseudo-niches may appear.

When *adhesions* occur between the duodenum and gall-bladder, the normal rounded curve of the duodenum is replaced by a persistent acute angulation. Cholecystography shows that the gall-

bladder is pulled medially, but has normal function.

The niche is pathognomonic of an *ulcer* in the *duodenum* and is the only absolute evidence of loss of substance from ulceration. When a proper technic is used, it is the most constant demonstrable sign. The characteristics of a penetrating ulcer are: (1) fixation of the cap; (2) a V-shaped deformity with a niche; (3) an accessory pocket; (4) divergence of mucosal folds into communicating channels; and (5) foreshortening. Although these may not all be seen in every case, penetration may be deduced if several of them are present.

Not all duodenal ulcers can be detected by x-ray examination, as small shallow ulcers and deep ulcers in which the crater is filled with blood clot may not retain the opaque medium.

*Deformities of the cap* are of importance. While they may be demonstrated in patients whose ulcers have healed and who are free from symptoms, they signify an alteration in the lumen of the cap, a potential or active cause of gastric dysfunction.

With the isolation and recognition of the *ulcer* niche, the nature of the lesion is evident and no other x-ray evidence is necessary for the diagnosis. If no ulcer niche can be isolated, the assumption that an ulcer is present in the duodenum at the time of examination is roentgenologically unjustified.

***Diverticulum of Duodenum.***—INCIDENCE.—Of 133 cadavers examined for duodenal diverticula, J. C. B. Grant (Canad. M. A. J. 33:258 (Sept.) 1935) found 15 that had single or multiple diverticula. None of the 10 subjects between 17 and 32 years of age had diverticula; 1 of the 20 between 33 and 42 years, and 1 of the 21 between 43 and 52 years had diverticula. Four of the 26 subjects between 53 and 62 years, 5 of the 30 between 63 and 72 years,

14 of the 19 between 73 and 82 years, and none of the 7 more than 82 years had diverticula. Of these subjects, 13 were male and 2 were female. For each decade after the fifty-second year the proportion of duodenum with diverticula remains almost constant, at about 1:5 or 6, whereas before this period the proportion is about 1:25.5. Of the 15 specimens with diverticula, 11 had 1, 3 had 2, and 1 had 3, making 20 diverticula in all. All save one sprang from the concave, pancreatic border of the duodenum, and all save this one were buried in the substance of the pancreas; and, had the duodenum not been filled with wax, a number of them would certainly have escaped detection. From the junction of the first and second parts of the duodenum there was 1 diverticulum. From the second part there were 14; of these, 8 arose around the entrance of the common bile and pancreatic ducts (perivaterine). From the junction of the second and third parts there were 2 diverticula, and from the third and fourth parts there were 3 diverticula. Though the diverticula were not sectioned and examined microscopically, it was in most instances apparent with the aid of a lens and probe that these diverticula were of mucous membrane herniated between the fibers of the circular and longitudinal muscle coats, which sometimes were carried on to the neck of the sac for a few millimeters. The specimen springing from the convex border of the second part was also of this nature.

**PATHOGENESIS.**—In duodenal diverticula this is obscure. L. Minucci del Rosso (Policlinico (sez. chir.) 42:236 (Apr.) 1935) states that the arguments for a mechanical origin are repeated through tradition but without conviction, and should be definitely abandoned. The dysontogenetic theory is also open to objections on anatomopathological grounds. Diverticula of the duodenum

are very probably congenital, but different in origin from diverticula of the large intestine. The author's tentative explanation of their formation is as follows:

At about the third or fourth week of embryonic life, the duodenal anlage, while undergoing canalization, is acted upon by extrinsic mechanical forces, *viz.*, compression by the pancreas and torsion of the umbilical loop. At the same time, a small number of accessory cavities normally appear on the dorsal side of the second portion. The latter are usually transitory, but it appears probable that in certain cases the extrinsic factors mentioned may lead to their persistence and exaggeration.

This hypothesis is strengthened by the facts that a very large percentage of duodenal diverticula are in relationship with the pancreas; the presence of pancreatic tissue in the walls of duodenal diverticula is not unusual; and 90 per cent. of duodenal diverticula occur in the second and third parts of the duodenum.

VARIETIES.—H. N. Fletcher and L. I. M. Castleden (Brit. J. Surg. 23:776 (Apr.) 1936) state that duodenal diverticula are of two kinds: primary and secondary. The secondary diverticula are due to traction from a neighboring inflammatory process and occur invariably in the first part of the duodenum. The primary diverticula, which are more common, are found in 75 per cent. of cases on the concave inner aspect of the descending part of the duodenum near the ampulla of Vater. They are thin-walled and usually consist of the mucosa and submucosa layers of the intestine. The opening into the bowel is usually from  $\frac{1}{2}$  to 1 cm. in diameter. The diverticula are hernias of the duodenal wall. Their location suggests a gradually developing protrusion through a weak spot in the wall near a blood vessel.

The authors report 3 cases in which the *diagnosis* was made by x-ray examination and *surgical removal* of the diverticulum resulted in cure.

**Tumors of Duodenum.**—C. E. Gardner, Jr., and D. Hart (J. A. M. A. 104:1809 (May 18) 1935) report a case of *enterogenous cyst* of the duodenum successfully treated by **permanent internal drainage into the intestinal tract**. In 6 similar cases collected from the literature the mortality was 100 per cent. Three of the collected cases were treated surgically, 2 by external drainage. In no case has the diagnosis been made before operation or autopsy. The symptoms are those of duodenal obstruction. As a rule, a palpable mass is found in the right upper quadrant of the abdomen. The probable origin of the cyst is an embryonic diverticulum.

A case of *adenoma* of the duodenum is reported by B. R. Sworn and J. Menton (Brit. J. Surg. 22:657 (Apr.) 1935) The patient's history and the findings of examination suggested only the presence of a gastric ulcer. At operation, the diagnosis of gastric ulcer was confirmed and the duodenal tumor was discovered unexpectedly. **Partial gastrectomy** was performed.

In a review of the literature the authors found that in a considerable number of cases of benign duodenal tumor the neoplasm was *associated with pathological lesions* elsewhere in the gastrointestinal tract, such as multiple polyps, carcinoma, cholelithiasis, and ulcers. The number of cases in which a duodenal tumor was the only lesion found has been so small that there is doubt whether such tumors have a characteristic syndrome. Symptoms, if present, are usually due to the associated lesions. The most common associated lesion is a peptic ulcer. Epigastric discomfort, pain of a colicky nature, nausea, and vomiting are therefore not infre-

quent. Attacks of diarrhea have been reported. Melena or the presence of occult blood in the stools appears to be the most constant feature of significance. Since these manifestations suggest peptic ulcer or carcinoma, the test meal and x-ray examination are important guides. X-ray examination, if successful, usually demonstrates a filling defect of the vacuolation type. Golden states that in the presence of a filling defect in the duodenal bulb, suggesting nonmalignant tumors, a 6-hour gastric retention may be considered evidence of a growth arising in the stomach and prolapsing into the duodenum, and the absence of such retention is indicative of a growth arising in the duodenum itself.

Adenomas of the duodenum are usually small and rarely cause intestinal obstruction. Because of the relatively fixed position of the duodenum, intussusception seldom results.

When the *associated* lesion is a *peptic ulcer*, **radical removal of the ulcer and tumor** is advisable. There is no recorded case of the development of malignancy in a simple duodenal tumor. When the lesion is *polypoid*, **transduodenal resection** should be sufficient. In the case of a *sessile tumor* or a tumor in which the possibility of *carcinoma* or *sarcoma* cannot be excluded, the **duodenum** should be **resected** and an **end-to-end anastomosis** performed.

Primary *sarcoma* of the duodenum is extremely rare. Only 61 authentic cases have been reported in the medical literature. D. Prey, J. M. Foster, Jr., and W. Dennis (Arch. Surg. 30: 675 (Apr.) 1935) claim it is usually of the round-celled type, but spindle-celled sarcomas, myosarcomas, and melanosarcomas have been described. The tumor originated in the muscularis or submucosa and grows longitudinally, infiltrating the intestinal wall and transforming the bowel into a solid and rigid tube. It seldom en-

croaches upon the bowel lumen sufficiently to cause obstruction. Ulceration of the tumor growth is rare as compared with carcinoma. The sarcoma grows to an enormous size. Its average weight is 500 grams. It appears as a smooth, gray, cylindrical mass covered by serosa.

The case reported by the authors was that of a man 48 years old, who was admitted to the Denver General Hospital on March 13, 1933, with a history of persistent nausea and vomiting of 3½ months' duration. Recently everything eaten had been vomited. About 1 month before entering the hospital the patient became conscious of a nontender mass in the upper part of the abdomen. In the last 3 months he had had a weight loss of 20 pounds. At no time had he passed tarry stools.

Physical examination revealed a palpable mass above the umbilicus extending into the right upper quadrant of the abdomen. The mass appeared to be the size of a grapefruit. It was movable, smooth, and very hard. Gastric analysis revealed no free hydrochloric acid. The total acidity was 5. On x-ray examination after a barium meal the stomach was found well filled and its greater curvature pushed upward from below by a rounded mass. The pylorus was normal. The duodenal cap showed dilatation, due to an obstruction in the second portion of the duodenum.

Operation disclosed a large mass the size of a grapefruit occupying the second and third portions of the duodenum and terminating abruptly at the duodenojejunal flexure. The mass was adherent to the pancreas posteriorly, and there were enlarged retroperitoneal glands. Removal of the tumor was impossible. The patient died April 27th, about 40 days after the exploratory laparotomy. Autopsy disclosed the presence of a large mass, occupying the second and third parts of the duodenum and weighing 695 grams. Microscopic sections showed the mass to be a lymphosarcoma primary in the duodenum.

In conclusion the authors state that no case of sarcoma of the duodenum has been cured by operation.

I. S. Startz (Radiology 25: 688 (Dec.) 1935) reports a rare case of *duodenal ulcer* of the supraampullary portion of the duodenum, *combined with* an independent primary *carcinoma* of the ampul-

lary portion of the duodenum; both of these lesions were visualized clearly in roentgenograms. The patient died from internal hemorrhage—an erosion of a blood vessel within the duodenal ulcer. There were no signs of intestinal obstruction present. The patient was 34 years old. Metastasis was present to adjacent lymph nodes and the liver. Brill states that metastasis even to the contiguous lymph nodes is not common. The patient was not jaundiced. Eger states that in cases of carcinoma of the ampullary portion of the duodenum, jaundice generally appears early. The x-ray study, if properly performed, is the strongest link in the chain of diagnostic methods. The well-trained roentgenologist should be capable of detecting an “organic” lesion in the small intestine. However, an attempt to specify the exact nature and site of the lesion is often a shrewd guess and may result in a fantastic x-ray diagnosis out of gear with that of the necropsy report. The presence of symptoms and physical observations suggesting a gastrointestinal malignant condition (including absence of free hydrochloric acid in gastric contents and presence of occult blood in stools), together with the recognition of a small intestinal organic lesion by the x-rays, should spell a preoperative diagnosis of carcinoma of the small intestine.

Malignant tumors of the small intestine constitute from 3 to 6 per cent. of all malignant gastrointestinal tumors. After discussing their clinical manifestations, x-ray characteristics, and gross pathological changes, H. P. Doub and H. C. Jones (Radiology 26:209 (Feb.) 1936) review 9 cases of *carcinoma of the duodenum*, 3 cases of *carcinoma of the jejunum*, 1 case of *sarcoma of the duodenum and jejunum*, and 2 cases of *carcinoid tumors* located in the jejunum and ileum, respectively. They report

several of these cases in detail to illustrate the various types of lesions.

*Carcinomas of the duodenum* occur anatomically as supraampullary, periampullary, and infraampullary lesions. They may all produce clinical signs of obstruction of the duodenum. Those of the periampullary type are associated, in addition with varying degrees of jaundice, depending upon the degree of obstruction of the ampulla. Pain is the most prominent symptom. Occult blood is almost always found in the stools. The x-ray changes vary from an irregular narrowing of the lumen to complete obstruction with a filling defect. The tumors are usually adenocarcinomas. Metastases occur with great frequency to the regional lymph nodes, liver and pancreas.

Primary *sarcoma of the duodenum* is very rare. Only about 60 cases have been reported in the literature. *Lymphosarcoma* is the predominating type. The growths attain a large size, with infiltration of the bowel wall, but with very little encroachment upon the lumen.

*Malignant tumors of the jejunum and ileum* have fewer localizing symptoms and signs than those of the duodenum. Obstructive symptoms and signs are the most common findings in this group of tumors. Obstruction may be caused by intussusception or by occlusion of the lumen by the tumor.

*Carcinomas of the jejunum and ileum* usually originate in intestinal polyps. They tend to ulcerate, undergo scirrhous change, and produce obstruction with the usual signs of that condition. A filling defect may also be present.

*Sarcoma of the small intestine* is most commonly found in the *ileum*, although it occurs also in the *jejunum*. The clinical findings do not differentiate it from carcinoma. Occasionally, a localized dilatation without obstruction is seen in the

roentgenogram. This is an aneurismal-like dilatation.

*Carcinoid or argentaffine-cell tumors* occur in all parts of the gastrointestinal tract, but are most common in the small intestine. They are of low-grade malignancy, and are said in some instances to be benign.

**JEJUNUM.—Tumors.**—*Carcinomas* of the jejunum are either annular constricting adenocarcinomas, which are the most frequent, or the less common polypoid carcinomas, which grow into the lumen of the bowel and frequently cause intussusception.

R. F. Carter (Ann. Surg. 102:1019 (Dec.) 1935) points out that every phase of carcinoma of the jejunum has been adequately treated in the literature except therapy, which is usually described as consisting of **excision**, when possible, with an **end-to-end** or a **side-to-side anastomosis**, depending upon the condition found at the operation. For inoperable cases, side-tracking operations alone are advised.

No well-devised plan has been advocated for the treatment of patients with jejunal obstruction. Such patients should be studied first to determine whether an alkalosis secondary to the vomiting is present.

The preoperative administration of from 3000 to 4000 c.c. (3 to 4 quarts) of fluid with 400 Gm. ( $13\frac{1}{3}$  ounces) of glucose and from 30 to 40 Gm. (1 to  $1\frac{1}{2}$  ounces) of sodium chloride is indicated in every case of high intestinal obstructions which does not show signs of sepsis. Frequent lavage or continuous intubation with a Levine tube during the *preoperative* period is of advantage to drain the proximal segment of the duodenum and jejunum.

In carcinoma of the jejunum at the ligament of Treitz or within 12 inches distal to it, there arises the necessity for particular consideration in performing

an anastomosis after excision of the segment of the gut containing the growth. The edema, hypertrophy, and dilatation of the gut proximal to the growth make an end-to-end anastomosis in this region difficult. The disproportion in the caliber of the two segments, the rapid peristalsis in this region, and the shrinkage of the proximal segment after operation tend to increase the danger of suture-line leakage. Under such conditions, **side-to-side union** is the procedure of choice. Because of the proximity of the ligament of Treitz there may not be sufficient jejunum below this point after excision of the tumor to permit a side-to-side anastomosis. In one of the cases reported by the author, the third portion of the duodenum was seen bulging to the right of the ligament of Treitz. This observation led Carter to adopt the following procedure:

The proximal jejunum is closed by inversion by a method similar to that commonly used on the duodenum in the Polya partial resection. The anterior leaf of the transverse mesocolon is incised to the right of the ligament of Treitz. This permits the third portion of the duodenum to prolapse into the operative field. The distal jejunum is swung counterclockwise to the right of the ligament of Treitz and then anastomosed side-to-side to the third portion of the duodenum. The upper edge of the slit in the mesocolon is sutured anteriorly to the duodenum, and the mesentery of the distal jejunum is stitched along its cut border to the peritoneum of the posterior abdominal wall.

The patient cited who was subjected to this procedure is alive and well 14 months after the operation.

**Jejunostomy with Jejunal Alimentation.**—J. A. Wolfer (Ann. Surg. 101:708 (Feb.) 1935) claims that up to within the last few years many attempts at jejunal alimentation were made, but most of them failed because of the use of an incorrect pabulum and a lack of understanding of gastrointestinal physiology. The records show that as early as 1885,

**jejunal alimentation** was recommended and used for the treatment of *carcinoma of the pylorus* and attention was called to the importance of placing the stomach and duodenum at rest in the presence of ulceration. In 1927, Henning made some interesting studies of the acid curve with jejunal alimentation in the presence of ulcer. He found that when a properly selected diet was used there was a marked decrease in the free and combined acid and in many instances the total gastric secretion was decreased. In an elaborate experimental investigation carried out in 1931, Scott and Ivy proved that a well-selected diet introduced into the jejunum would maintain an animal in a proper nutritional state for many months and prolong the latent period during which no acid was secreted. During a period of 9 hours of continuous jejunal feeding, no hunger contractions occurred. The gastric phase of gastric secretion was eliminated by withholding everything by mouth. The pabulum consisted of **water**, 3000 c.c. (3 quarts); **cane sugar** 150 Gm. (5 ounces); **peptone** (dried), 100 Gm. ( $3\frac{1}{2}$  ounces); **wheat flour**, 300 Gm. (10 ounces); **whole milk**, 2000 c.c. (2 quarts) and **cream** (20 per cent. fat), 1000 c.c. (1 quart); with sufficient **salt** to maintain the chloride balance and such vitamins as are contained in **cod-liver oil**, **viosterol**, **yeast**, and **citrous juices**. The observations made in these experiments suggested that in the human being excessive acid secretion might be reduced by adequate jejunal alimentation and the stomach placed at rest by continuous jejunal feeding.

In the procedure followed by the author a *Witzel jejunostomy* is used, the jejunal catheter is inserted at least 8 inches into the lumen of the jejunum, and the gut is fixed to the abdominal wall. The catheter is drawn through a stab wound on the left side of the ab-

domen or through the lower end of the laparotomy incision if the latter is made on the left side.

Considerable care is necessary in jejunal feeding. The pabulum must be introduced slowly to simulate the emptying of the stomach. In the authors' cases it is given with a specially designed electrically driven pump which will deliver any quantity desired during a specific time. Three or four hours after the jejunostomy, water is slowly introduced, 100 c.c. or less being given per hour. The pabulum feedings are begun after 12 hours. The Ivy pabulum, modified to meet the requirements of the individual case, is used. During the first 24 to 48 hours, it is diluted with equal parts of water. Feedings are given every hour during the day and night. Each feeding required from 15 to 30 minutes, depending upon the amount, the time after jejunostomy, and the response of the patient to the feeding. Too large amounts administered too rapidly will be followed by cramps and diarrhea. In some instances the fat content may be too high, causing bowel irritability, or the patient may not tolerate the amount of orange juice given. To determine the ideal diet the tolerance of the particular patient must be established. With care and patience it is possible to provide a well-balanced daily diet which will supply from 3000 to 3600 calories and vitamins to prevent avitaminosis.

The *indications* for jejunal alimentation are:

1. Larger ulcerations of the stomach which are not resectable. Jejunal alimentation favors healing of such ulcerations by placing the stomach at rest and abolishing acid gastric secretion. The author cites a case.

2. Carcinoma of the stomach. The distressing symptoms, pain, hunger, and thirst due to carcinoma, can be con-

trolled better by jejunal alimentation than by any other means. The author cites a case.

3. Carcinoma of the lower end of the esophagus. Jejunostomy is preferable to gastrostomy in this condition, because it relieves the pain incident to the involvement of the cardia which is present in many cases. A case is reported.

4. Duodenal ulcer with acute exacerbations associated with excessive vomiting and marked nutritional disturbance. Because of the persistent vomiting, the nutritional state of the patient becomes a vital problem. Moreover, the large amounts of alkalis administered and the loss of chlorides incident to the vomiting often lead to alkalosis. In many cases the duodenal tube is prevented from passing through the pylorus by organic obstruction due to the ulcer or by spasm. In such cases jejunostomy affords a means of nourishing the patient and supplying minerals and vitamins to maintain a proper nutritional and chemical balance and the physiological effect of jejunal feeding favors healing of the ulcer. A case report is cited.

5. Gastrojejunal ulcer. Because of the critical condition of the majority of patients with gastrojejunal ulcer and the technical difficulties encountered at operation for this lesion, jejunal alimentation is recommended to improve the patient's nutritional state and allow the acute symptoms to subside so that operation may be carried out at a time when it is more likely to be successful.

6. Complementary jejunostomy. Jejunal alimentation is indicated: (a) to control dehydration and starvation and associated chemical changes after gastroenterostomy followed by persistent vomiting (a case is cited); (b) to provide the poorly nourished patient with sustenance and favor healing at the anastomosis after gastric resection; and (c) in miscellaneous cases in which at the

time of operation it appears likely that persistent postoperative vomiting will occur (a case of acute pancreatitis with fistula and evisceration is cited).

7. Linitis plastica.

8. Excessive trauma to the stomach.

9. Pernicious vomiting after gastroenterostomy.

10. Extragastric or duodenal lesions associated with marked nutritional disturbances and excessive vomiting; pancreatitis; cases of long-continued drainage of the gall-bladder or common duct with nutritional disturbances; and the pernicious vomiting of pregnancy.

11. Selected cases of gastric and duodenal hemorrhage.

**ILEUM.—Regional Ileitis.**—In discussing this condition, A. J. Rosenblate, A. A. Goldsmith and A. A. Strauss (J. A. M. A. 106:1797 (May 23) 1936) state that for many years a number of granulomatous conditions of the intestine possessing common symptomatic and pathological features have been described. At first they were mistaken clinically and microscopically for malignant conditions, but later were proved to be benign, inflammatory lesions. In 1932 they were described as a distinct entity by B. B. Crohn under the term "*regional ileitis*." A year later Harris suggested the term "*cicatrising enteritis*." No definite etiological factor or factors have been isolated. The usual site is the terminal ileum, but other portions of the intestine may be involved.

Pathologically, the condition is one of proliferation of the hematopoietic cells and proliferation and irritation of the somatic cells of the intestinal wall. Later there is ulceration with fibrosis, narrowing of the intestinal lumen, and a tendency toward perforation and fistula formation. Clinically, regional ileitis is characterized by dull pain in the right lower quadrant of the abdomen, a low grade intermittent fever, slight diarrhea,



anorexia, anemia, and a rapid pulse. X-ray examination by the technic of Kantor is the most important means of establishing the *diagnosis*. A helpful sign is the "string sign"—a thin slightly irregular linear shadow suggesting a cotton string in appearance, which extends from the region of the last visualized loop of ileum through the entire extent of the filling defect and ends at the ileocecal valve.

Medical treatment is usually unsatisfactory. **Surgical treatment** is the treatment of choice. The case reported by the authors showed the typical clinical and x-ray picture of the condition, with added involvement up to, but not including, the distal portion of the transverse portion of the transverse colon. The patient made an uneventful recovery. For the condition in which the pathological changes extend to the colon the authors suggest the term "*ileocolitis ulcerosa chronica*."

The experience of B. B. Crohn and B. D. Rosenak (*Ibid.* 106:1 (Jan. 4) 1936) covers 60 operatively diagnosed cases of ileitis and it seems essential to recognize another less common form of terminal ileitis that is associated with an inflammatory and ulcerative colitis. The first case of the combined disease was reported in 1934 by Colp.

All of the authors' 9 patients with ileitis and colitis were young persons. The outstanding clinical characteristics of the condition are pain and a mild diarrhea. At first, the course may be either acute or fulminating, but eventually it assumes a chronic phase. In all cases the ileum and the colon are typically involved. In some, the colitis is apparently continuous with the ileitis. In others, the colon involvement is patchy or segmental. The *diagnosis* rests on careful and accurate x-ray studies made with a barium meal and a barium enema. As a rule, the right ascending

colon up to the transverse colon, and sometimes with the latter, is involved, the distal colon being free from the disease. Occasionally spontaneous recovery of both lesions occurs. The ileitis is the dominating feature of the disease, its removal usually resulting in cure. A side-tracking operation without removal of the diseased ileum is ineffectual. The brilliant surgical results seen after **resection** of primary regional ileitis may not always be duplicated in the more complicated collateral involvement of the ileum and colon. With greater experience and more watchful direction, early recognition and early resection may, except in acute cases, yield the solution to an otherwise complicated and difficult problem.

In an article by K. A. Meyer and P. A. Rosi (*Surg. Gynec. and Obst.* 62:977 (June) 1936) symptomatology and treatment of regional ileitis is stressed. They point out that the *symptomatology* varies with the different phases of the pathological process and with the location of the lesion. The symptoms in the acute types of regional enteritis, particularly of the ileum, usually simulate an acute appendicitis. The symptoms in the chronic forms mimic a low-grade intestinal obstruction or ulcerative colitis. Persistent external intestinal fistulas develop following drainage of an intraabdominal abscess which is a sequel of the regional enteritis. The lesions higher in the intestinal tract tend to give symptoms of an intestinal obstruction more frequently and more rapidly than lesions in the ileum or colon. The *diagnosis* in the acute types of regional enteritis is usually made at operation undertaken for an acute appendicitis or an "acute surgical abdomen." In the authors' series of cases the symptoms in the patients with an acute regional enteritis were those of an acute incomplete intestinal obstruc-

tion. The physical findings corresponded closely to those of an acute appendicitis. This association of symptoms and physical signs of acute intestinal obstruction and acute appendicitis may be an aid in establishing the diagnosis of an acute regional enteritis. The diagnosis of chronic types with stenosis of the bowel is usually made by x-ray examination which shows a filling defect in the involved intestine.

The *treatment* of regional enteritis varies with the phase of the pathological process. Acute regional enteritis limited to the bowel and not associated with thickening of the mesentery may resolve spontaneously. If, however, the mesentery is thickened and indurated, it is probable that ulceration of the mucosa has extended into the mesentery; spontaneous resolution then is less likely to occur, and a **shortcircuiting operation** or a **resection** is indicated. Chronic regional enteritis with stenosis is best treated by resection or a shortcircuiting operation. When complicated by an external intestinal fistula, resection of the involved bowel with the fistulous tract is necessary to close the fistula.

**Tumors of Ileum.**—W. Cossmann (Beitr. z. Klin. d. Tuberk. 88:1 (May 18) 1936) states that most reports about *tuberculous ileocecal tumors* take up the difficult diagnosis and the surgical therapy of this disorder but neglect the *anatomic-pathologic aspects*. He reports several necropsies. The first case had an extremely chronic course. The necropsy revealed that, in addition to the ileocecal region, a portion of the ileum was involved. The lungs contained no signs of a former tuberculous process, and it is assumed that the primary complex had been in the intestine rather than in the lungs. However, the most noteworthy aspect was that granuloma formation and caseation were absent. The bacilli were of the bovine type,

which is considered further proof that the primary focus was localized in the intestine, and were present in unusually large numbers, appearing not only in small foci of the submucosa and of the mucosa, but also on the free surface of the intestinal lumen. Their virulence was low. The author thinks that in this case a strain of bovine tubercle bacilli of low virulence attacked an organism which, in the beginning, had considerable defense powers. However, in the course of the disease the local resistance became reduced, and this explains the considerable proliferation of the bacteria.

Cossmann (*Ibid.*) further describes a group of 4 cases of tuberculous ileocecal tumors. This group differs from the first case in that all these patients had a severe pulmonary tuberculosis. In 2 patients the gastrointestinal symptoms predominated from the beginning, whereas in the other 2 they appeared only during the advanced stage of the pulmonary tuberculosis. The appendix was given especial attention and numerous cross sections were examined. In this connection the author cites several cases reported by Glogauer. These cases demonstrate clearly the dependence of ileocecal tuberculosis on the disease processes of the appendix. The author believes that the dissemination of tubercle bacilli from the diseased appendix to the adjoining cecum may be a causal factor in some of the cases.

A case of *carcinoid tumor of the lower ileum* is reported in detail by W. Q. Wood (Brit. J. Surg. 23:764 (Apr.) 1936). Though carcinoid tumors are relatively common in the appendix, only a few more than 150 occurring in the small intestine have been recorded. Metastasis to the regional lymphatic glands is extremely rare in the region of the appendix, and distant metastasis is practically unknown. Carcinoids in the small intestine are much more malig-

nant than those in the large intestine. Secondary growths from the former have been found frequently in the regional lymph glands and occasionally in the liver, lungs, and other organs.

The clinical picture of carcinoid tumor of the small intestine is that of slowly progressing stenosis of the bowel. From the clinical syndrome it is practically impossible to differentiate an intestinal carcinoid tumor from adenocarcinoma. The striking features of the carcinoid tumor are the yellowish color of its cut surface and the presence of silver-reducing granules in the cytoplasm shown on microscopic examination.

The average age of patients with a carcinoid tumor of the appendix is under 30 years, while that of patients with a carcinoid tumor of the small intestine is between 50 and 60 years. Regional metastasis has occurred in about 25 per cent. of cases of carcinoid tumor involving the small intestine. In cases of adenocarcinoma of the small intestine the average frequency of metastasis is at least 10 per cent. higher. The *treatment* of a carcinoid tumor, like that of an adenocarcinoma, is **radical operation**.

**CECUM.**—*Circumscribed phlegmons* of the cecum are described by H. Pich (Beitr. z. klin. Chir. 161:107, 1935). In the simplest form of nonspecific inflammation of the intestinal wall, *pericolitis*, the wall of the intestine shows delicate deposits or indurated strands which are to be regarded as the sequelæ of an inflammation of the wall which has run its course. When the disease lasts for a considerable length of time, the involved part of the large intestine takes on a tumor-like appearance and its lumen is definitely narrowed by the thickening of the wall resulting from the chronic inflammation. The tumor-like formation occurs most frequently in the cecal region and often involves

also the lowermost coils of the ileum. Clinically, the disease cannot be distinguished from a specific condition such as actinomycosis, tuberculosis, or cancer. It has been attributed to traumatization of the mucosa by foreign bodies or intestinal parasites and to metastatic infarction following septic systemic diseases or purulent bronchitis. In the majority of all nonspecific inflammations of the large intestine a pathological change of the mucosa is to be regarded as the cause.

The *treatment* of circumscribed phlegmons of the intestine must depend upon the extent and nature of the inflammation. All chronic inflammatory tumors of the large intestines must be removed, as recovery of the intestinal wall cannot be counted upon. Nordmann says that *when the focus is small and circumscribed, the intestinal wall may be sewed over it and the focus cut out*. Phlegmons of greater extent require **resection**. Tamponade is to be rejected. Phlegmons of the cecum and the ascending colon are to a great extent capable of spontaneous healing. The author observed *spontaneous recession* even in 3 cases in which the phlegmons had involved the intestinal wall to a considerable extent. He regards the routine performance of ileocecal resection as too radical. In 1 of 3 of his cases in which healing occurred without resection an intestinal fistula formed, but was closed by operation later.

J. H. Powers (Ann. Surg. 103:279 (Feb.) 1936) calls attention, by the use of 3 clinical reports, to the *interrelationship of inflammatory lesions of the terminal ileum, appendix, cecum, and ileocecal lymph nodes*. The first patient had diffuse inflammation of the terminal ileum, appendix and cecum, and secondary involvement of the ileocolic nodes in the mesentery; in the second case the tip of an inflamed appendix was ad-

herent to a mass of enlarged mesenteric nodes; the third case was one of primary typhlitis with localized, ulcerative, inflammatory changes in the wall of the cecum. Regional ileitis, acute nonspecific inflammation of the cecum, and mesenteric lymphadenitis in the ileocolic angle are discussed. In view of (1) the similarity between the lymphatic apparatus of the appendix and terminal ileum, (2) the frequency of mesenteric adenitis as an accompaniment of regional ileitis, and (3) the lack of interest in the ileocolic nodes in the presence of obvious appendicitis, it is quite possible that these nodes are involved more frequently than is generally suspected. The author believes that the prompt subsidence of symptoms following appendicectomy in Wilensky's early cases, in the cases reported by Rockey, and in his first 2 cases, and the anatomic relationship of the lymphatic channels of the appendix to the ileocecal lymph nodes, suggest that the appendix does play some part in the etiology of this form of glandular inflammation.

**Volvulus.**—Volvulus of the cecum, both acute and chronic, has been studied by R. H. Sweet (New England J. Med. 213:287 (Aug. 15) 1935). Records at the Massachusetts General Hospital show only 6 cases of volvulus of the cecum. Sweet reviews these cases and reports 2 personal cases in detail.

In the first of Sweet's cases operation was performed 2 days after the onset of symptoms of acute intestinal obstruction. The cecum was not attached to the posterior abdominal wall and was completely rotated. After reduction of the volvulus, the cecum emptied into the ascending colon. **Cecostomy** was followed by uneventful recovery.

The second case was that of a patient with an intermittent volvulus of the cecum. The cecum was freely movable and unattached to the posterior abdom-

inal wall. It was found to be rotated one-half turn in a clockwise direction. The terminal ileum was fixed by adhesions to the fossa normally occupied by the cecum. Correction of the volvulus and fixation of the cecum into its normal position led to uneventful recovery.

Sweet found no case reported in the literature in which a correct *diagnosis* was made before operation. The one possibly suggestive sign is localized distention on the right side. In the chronic recurring type the history may suggest the condition and x-ray examination may be of aid in the diagnosis.

In the *acute type*, **immediate operation** is indicated to correct the volvulus, relieve the obstruction, and, if possible, prevent recurrence. This is best accomplished by **detorsion of the cecum followed by cecostomy**. In the *chronic type* the aim of treatment is **correction of the deformity** and the **prevention of recurrence**. The results of surgery are good except when resection or excision is performed in acute cases.

**Cecoplication.**—F. Placeo and F. Stoppani (Clin. chir. 11:323, 1935) report 12 cases of *atonic cecum* diagnosed roentgenologically in which cecoplication was performed. They conclude that cecoplication does not alter the anatomy of the ileocecal region and is frequently followed by improvement in the function of the cecum.

**COLON.—Nerve Supply.**—Knowledge of the autonomic nervous system is still very incomplete. Surgical intervention has far outstripped anatomical and physiological knowledge. As a result, operations based on false conceptions have done much to discredit legitimate surgery of the autonomic nervous system. The practical advantage and importance of an exact knowledge of the anatomy of the autonomic nerves are obvious. This discussion by G. A. G.

Mitchell (Edinburgh M. J. 42:11 (Jan.) 1935) of the innervation of the distal colon is based on dissections of 15 stillborn babies.

In summarizing the author states that the distal colon receives its nerve supply from two main sources: (1) the inferior mesenteric plexus, and (2) the hypogastric nerves and plexuses. The former supply is mainly and possibly entirely sympathetic in nature. In the latter there may be both sympathetic and parasympathetic fibers, but para-sympathetic elements predominate.

**Megacolon.**—The association of *megacolon with a hypotonic bladder* in 3 cases is discussed by J. W. Watts and C. A. W. Uhle (Urol. and Cutan. Rev. 40:244 (Apr.) 1936). A huge colon was demonstrated by barium enema in each, and in each a hypotonic bladder was revealed by cystometric examination, the bladders accommodating 600, 800 and 1000 c.c., respectively. The association of megacolon and dilatation of the bladder which is described in 5 per cent. of the cases, is considered by some authors indisputable evidence of a *neurogenic origin*. Improvement of function of the colon and bladder which follows presacral sympathectomy further supports the neurogenic theory. Experimental megacolon has been produced by removal of the parasympathetic nerve supply to the distal colon.

One of the patients had a lesion of the brain, involving the cerebral cortex and the basal ganglia. Since it has been shown that an alteration of tone and function of the bladder and gastrointestinal tract may be produced by lesions in the brain, the huge colon and the hypotonic bladder is attributed by the author to a disturbance of the representation of these viscera in the brain. The not infrequent occurrence of megacolon in patients with acromegaly indicates that the growth hormone of the

pituitary gland is sometimes a factor. The personality of the individual may also be of influence, since megacolon is more frequent in the schizoids than in other groups.

At the present time, motor, sensory and reflex changes are almost entirely depended upon for evidence of involvement of the central nervous system. The methods used for examination of the autonomic nervous system are relatively crude. The authors believe that more careful examination of the bladder and bowel through a closer coöperation of the neurologist, urologist and gastroenterologist will result in an increase of knowledge of the autonomic nervous system. Many conditions that are now considered functional, probably, in the light of new knowledge, will tomorrow be considered pathological.

**Partial sphincterectomy** in the treatment of megacolon is suggested by E. Etzel (Rev. brasil. de cir. 5:95 (Mar.) 1936). The author says that the pathogenesis of *sphincter achalasia* (failure of one or several of the sphincters of the large intestine to relax), due to disturbances of the Auerbach plexus in megacolon, is proved. The treatment by partial resection of the involved sphincter or sphincters gives satisfactory results.

Correia Netto's technic consists in resecting a third of the circumference of the involved sphincter in all its extent, including a segment of 2 cm. of the muscular layers above the sphincter, in order that all the circular fibers of the given sphincter are divided by resection and none of them are left forming an unbroken ring.

*Resection of the internal sphincter of the anus* is performed with the patient under **epidural anesthesia** by the following technic: Curved incision of the skin at 1.5 mm. on left side of the anus beginning and ending at the perineal raphe; dissection of the internal and external sphincter of the anus; exteriorization of the internal sphincter through the operative wound and resection of the sphincter in a

third of its circumference up to the muscular layers; reconstruction of the operative wound and drainage.

*Resection of the pelvirectal sphincter* is performed with **spinal anesthesia** by infra-umbilical median laparotomy with the following steps: Traction of the pelvic colon (having the third sacral vertebra as a point of reference for localization of the pelvirectal sphincter); performance of a 10 cm. longitudinal incision on the sphincter; and resection of the latter in a third of its circumference. It is advisable to take care during this step not to injure the mucosa. The gap in the colon left by resection is covered with a flap from the omentum, which is sutured to the border of the gap for peritonization. The wound is closed without drainage.

Recovery was obtained in 2 patients by partial resection of the internal sphincter of the anus in one case and of the pelvirectal sphincter in the other case. In a third case recovery followed partial resection of both the pelvirectal and the internal anal sphincters.

**Mobile Colon.**—C. C. Cade (Texas State J. Med. 31:689 (Mar.) 1936) has been through the gamut of attacking a chronically inflamed appendix and of dilating supposed strictures of the ureter without relief of right-sided abdominal pain. Later, he began to study ptosis with the free and movable colon and its treatment, as advocated by Waugh and Coffey. He did not obtain the results to which he believed the patient was entitled, but some relief was secured in the majority of cases. This caused him to think that there was some value in what was being done, but as yet the proper attack has not been made. Then one day he operated on a woman suffering from acute pain in the right side, severe enough to require morphine for relief. He had previously removed the appendix during a hysterectomy for fibroid tumor. The patient did not have intestinal obstruction, because a barium sulphate meal went through the intestine in the proper period of time. A pendu-

lous mobile colon twisted on itself was found. There was a distinct twisting to the left of the colon, just below the hepatic flexure, with subsequent kinking of the ileum at the ileocecal valve. The condition was not severe enough to cause obstruction and the intestine was normal in color. Three interrupted sutures were taken **through the lateral white line of the cecum to the parietal peritoneum** and tied. This was sufficient to give a hobbling effect to the colon, but certainly not enough to support its weight and prevent ptosis. It did give, however, a straight terminal ileum, so that it entered the colon approximately at a right angle as it should and was sufficient to prevent the intestine from twisting on itself again. The patient has had no recurrence of symptoms in 6 years. Since that time the author has been doing this simple operation in cases in which right-sided pain could not be attributed to other causes, with the result of apparently complete relief from the pain, generally a cessation of the nervous symptoms, and a gain in weight. Because of this fact, the writer concludes that it is not the ptosis of the intestine or the ptosis of the ascending colon that is causing the trouble, but rather the rotation permitted by its insufficient attachments, with resultant twisting and narrowing of the lumen of the intestine just below the hepatic flexure and more or less ballooning or dilatation of the head of the intestine, accompanied by kinking of the terminal ileum caused by twisting of the intestine.

**Ulcerative Colitis.**—A report on a series of 149 cases of chronic idiopathic ulcerative colitis seen during the past 20 years in the wards of the Massachusetts General Hospital is given by L. S. McKittrick and R. H. Miller (Ann. Surg. 102:656 (Oct.) 1935). The patients were all studied with particular

reference to the value of, and indications for, surgical treatment. Every patient not responding to medical treatment was seen in consultation with a surgeon. Operation, if advised, was usually an **ileostomy** with complete external diversion of the fecal stream. In a few cases in which the disease was localized, a more distal procedure was carried out.

Variations in *symptoms* have resulted in occasional uncertainty as to *diagnosis*, particularly in the more acute cases. Rectal bleeding is an almost constant sign. Described as "streaks of blood," it occurred in 87 per cent. of the cases. Massive hemorrhage occurs in about 5 per cent. of cases and is often a serious symptom. Diarrhea occurs frequently without blood at the onset and is present in all cases at some stage of the disease. Constipation is not uncommon, especially prior to the onset of acute symptoms. In one of the cases reviewed, constipation alternated with diarrhea. The patient finally came to the hospital because of bleeding and failure of the bowels to move for 5 days. The onset may be sudden or gradual. In some cases a sudden chill and high fever initiate the attack. Recurring attacks of fever, marked prostration, rapid loss of weight and strength, and a tendency toward remissions and relapses are characteristic. Complications are frequent and may be serious. Perianal infections, polyneuritis, hemorrhage, and later polyposis, are commonly sequelæ of the disease. Physical examination may reveal tenderness along the course of the colon. Laboratory examinations are important. *Proctoscopy* represents the most important single method of examination. In all of the cases reviewed its findings were positive. The outstanding characteristic is the diffuseness of the process. The red, granular, edematous mucous membrane, bleeding easily on

slight trauma, may be studded with small white dots representing small miliary abscesses which later break down to form superficial ulcerations. The ulcerations may be seen only with great difficulty or may coalesce to form lesions 1 or 2 cm. in diameter. Next to proctoscopy, the most valuable diagnostic aid is *x-ray examination with a barium enema*.

In the 149 cases reviewed, there were 27 deaths, a mortality of 18 per cent. The chief causes of death were general peritonitis from perforation of the colonic ulcers, widespread sepsis, pneumonia, and abscess formation in the liver.

**TREATMENT.**—The authors believe that the only surgical procedure indicated in ulcerative colitis is one which will give complete rest to the affected bowel segment by diverting the fecal stream externally proximal to the disease. With few exception, this means **ileostomy**. In carefully selected cases, surgery has an important place in the management of intractable and serious ulcerative colitis. Ileostomy is the operation of choice. Preceded and followed by **blood transfusions**, it is frequently a life-saving procedure. It was ultimately performed in 40 per cent. of the cases reviewed. Approximately 40 per cent. of the patients surviving ileostomy will later require removal of the diseased colon. The results after **subtotal colectomy** are excellent.

According to R. B. Cattell (J. A. M. A. 104:104 (Jan. 12) 1935), surgical treatment is of value in ulcerative colitis, particularly in the chronic cases complicated by fistulas, intestinal obstruction, and recurrences of the acute exacerbations of the disease. In these cases the colon has little possibility of carrying out its function and serves as a constant source of infection. **Transverse ileostomy** may result in a remis-

sion. When performed, it must be considered permanent. It is of greatest value in the chronic cases, but may be necessary in the acute cases. **Complete colectomy** may be necessary for relief and can be done with a low operative mortality if performed in divided operations. It has been carried out in 3 patients, who have remained well for 1 year. **Partial colectomy** can be done in selected cases if the involvement is definitely limited to one segment of the colon. It was performed in 6 patients in this series. Ileostomy and colectomy are not suggested to replace the medical treatment of ulcerative colitis, but are presented as an aid in the management of the intractable and complicated cases.

Twenty years ago ulcerative colitis was regarded as a disease belonging entirely to the field of internal medicine and the surgeon was called on only to treat certain complications that arose. The large number of methods of treatment employed today and the high mortality rate still prevailing make it obvious that the ideal method of treatment has not yet been found. C. A. Kunath (Arch. Surg. 32:302 (Feb.) 1936) states that the surgical procedures that have been developed have one of the following purposes: (1) the provision of an avenue for direct irrigation of the diseased bowel (*e. g.*, **appendicostomy**); (2) the establishment of a condition of physiological rest for the diseased bowel by diversion of the fecal stream (**ileostomy**); or (3) eradication of the disease (**partial or total colectomy**). On the whole, the results are still far from encouraging. While ileostomy is the accepted treatment in most clinics, the more radical colectomy appears to be gaining favor.

During the past 4 years Kunath has treated a number of cases by the more conservative **cecostomy** or **appendicos-**

**tomy** with subsequent **irrigation** of the diseased bowel **through a tube**.

To evaluate the relative merits of the various operative procedures, he studied 35 cases of chronic ulcerative colitis. He has found appendicostomy and cecostomy with subsequent irrigation of the diseased bowel segments useful procedures in selected cases. In 18 cases in which this type of treatment was used the typical course was one of immediate improvement. However, this improvement is usually too encouraging, because it does not accurately portray the end-result. After about 1 year, it usually ceases. If the patient stops the irrigations, his general condition rapidly declines. X-ray examination shows the colon continuing to narrow and foreshorten and gradually becoming of the "garden-hose" type. Cure results rarely, if ever. Kunath prefers to regard the irrigation type of therapy as a compromise between strictly medical treatment and ileostomy. It seems to be a safer operation with less discomfort to the patient than ileostomy. The patient should not expect a cure and should be prepared to accept the tube as a permanent handicap. Moreover, he must face the possibility that more radical surgical intervention may be necessary later. Cecostomy and appendicostomy improve the general condition and render the patient a better risk for subsequent more radical surgery. They are contraindicated when the disease is in the acute phase with many stools and a high fever, as irrigations at this time may provoke further bleeding and even spread the disease. There is no ideal method of treatment that can be applied routinely to all cases. Kunath believes that at the present time surgery has something definite to offer, but the procedure used must be that which best meets the requirements of the individual case.



**Diverticulitis of Colon.**—DIAGNOSIS.—J. Masson (Rev. méd. de la Suisse Rom. 56:154 (Mar. 10) 1936) is convinced that diverticulitis of the colon occurs more frequently than has been supposed, as he has seen 4 cases within a relatively short time. Statistics on the incidence of the condition from different clinics vary widely, undoubtedly because of differences in the technic of the x-ray examination. The symptoms of the disease also vary and do not suggest the diagnosis. In 2 of the author's cases the presence of a carcinoma of the colon was suspected before x-ray examination.

The use of the opaque meal is rarely sufficient to show diverticulitis of the colon. However, in one of the author's cases it suggested the presence of the condition and the diagnosis was later confirmed by the use of an opaque enema. The procedure followed in Masson's cases is as follows:

The evening before the examination is to be made, **castor oil** is administered unless there is some clinical contraindication to the use of a purge, and an **enema of plain warm water** is given. Another warm water enema is given about 1½ hours before the x-ray examination. The enemas must be given carefully and under low pressure.

The **opaque enema of barium or thorium** is given under fluoroscopic control. While this fluoroscopic study is necessary, it does not always reveal the presence of diverticulitis. At least 2 x-ray pictures are taken, one when the colon is filled with the opaque substance and the other when the opaque enema has been largely evacuated, to show the mucosa in relief. In some cases the diverticulum filled with the opaque medium is seen distinctly. In others, the image is less clear, being obscured by spasm of the colon. Under the latter circumstances the x-ray pictures taken after evacuation of the opaque enema is of special value.

The clinical diagnosis of diverticulitis is of importance, especially in cases in which the symptoms resemble those of carcinoma. Diverticula are found most

frequently in the descending colon, especially the sigmoid.

**Villous Tumors of Colon and Rectum.**—H. Junghanns (Ergebn. d. Chir. 38:1, 1935) reports a continuation of the investigation begun by Schmieden and his coworkers concerning the etiology of cancer of the large intestine. It demonstrates that polyps are of etiological importance in this cancer since, of 130 operative specimens, 70 per cent. showed an unquestionable relationship to intestinal polyps. Of the cancers of the colon and rectum which developed from polyps, only 27 belonged to the villous tumor group. These 27 lesions and 1 previous cancer were subjected to exact pathologicoanatomical and clinical investigation. The findings are reported with detailed clinical histories and 51 illustrations, the most interesting of which are the roentgenograms. The latter show a characteristic surface picture since, because of the segmented and cleft surface, the opaque medium produces corresponding opaque and transparent shadows.

*Classification* of villous tumors according to their benignancy or malignancy resulted in the recognition of 3 groups: (1) those which are absolutely benign; (2) those with precancerous changes in the epithelium, always in the middle part; and (3) malignant tumors. The first indication of the formation of a true cancer is the appearance in the center of an ulcer with a hard base (in 24 of 28 cases). In half of the cases there was a colloid cancer. The villous tumors are to be placed in Group 2 of the Schmieden-Westhues classification. In cases of villous tumor there is usually a long history of an especially copious and annoying discharge of mucus so that the patient has frequently been treated for colitis. As a rule, the lesion is situated low in the rectum.

Because of the tendency toward malignant degeneration, the treatment should always be radical, as in carcinoma.

F. W. Rankin (Ann. Surg. 102:707 (Oct.) 1935) gives an additional report of a series of 5 cases of colectomy for *diffuse adenomatosis and complicated chronic ulcerative colitis*. Six cases were reported previously in which the entire colon and rectum were removed by multiple procedures. In 4 of the present series the colon was removed down to the rectosigmoid juncture; in the other, total colectomy was done. In 2 cases of the chronic ulcerative colitis variety it is probable that the rectum will have to be removed subsequently, although the patients show marked improvement. In one case, the reestablishment of the continuity of the gastrointestinal tract was carried out at the third stage following destruction of the rectal polyps by fulguration. There was one operative death following the second stage colectomy; in this case fulguration had been carried out on the rectal polyps and the plan was to transplant it subsequently at a third maneuver into the terminal ileum. The disappearance of diffuse rectal polyps following vigorous fulguration is surprising and encourages the belief that this plan, which has heretofore been considered an alternative one and available only when the rectal polyps were few, may be available to a great many more of these cases. Technical steps of importance are the preservation of the omentum in the chronic ulcerative colitis group and in the case of adenomatosis when there is no suggestion of a malignant condition. A second technical point of advantage is the method of handling the *rectal stump*, which turns in with difficulty in many of the polyposis cases and not at all in the chronic ulcerative colitis variety. The stump must be

closed over as accurately as possible, covered with whatever tissues are available and, if there is any question of leakage, wrapped in iodoform gauze and a rubber tissue to establish a drainage track in the event that the suture line fails to hold. Of the 11 patients, 1 died 18 months following the complete operation from recurrence of carcinoma, which had developed on the polyps and which was diagnosed at exploration. A second patient died 2 years later following a hysterectomy performed elsewhere. One patient died in the hospital following the second stage operation, and the remaining 8 patients are alive and well and have all returned to their various occupations.

**Carcinoma of Colon.**—SYMPTOMS AND DIAGNOSIS.—According to E. E. Shaw (J. Iowa M. Soc. J. 25:528 (Oct.) 1935), the symptoms and signs of carcinoma of the *right half of the large intestine* are not diagnostic but suggestive. They are: pain, usually a dull inconstant pain, fairly well localized to the right side; indigestion of a vague type; anemia and weakness, the anemia being marked, with a red count often near 3,000,000, a decreased hemoglobin, and a picture suggestive of pernicious anemia; change of intestinal habit of the patient, whether constipation, diarrhea, or alternation of the two; occult blood in the stool, which is a fairly constant finding, but melena is usually a late symptom in lesions of the right colon; a tumor mass in the right abdomen, usually movable and somewhat tender, which is often found and is the presenting symptom; loss of weight and cachexia as late manifestations, usually meaning a far advanced case, and x-ray observations.

Signs and symptoms of carcinoma of the *left half of the colon* are: obstruction, either complete or partial; change in the intestinal habit, again the most

constant symptom, being usually a progressive constipation; blood and mucus in the stools of practically all these patients; rumbling, visible peristalsis; the feeling and hearing of gas and liquid feces as they pass through the constricted portion of the colon, which is frequently noted and the patient may even be able to localize the lesion by these symptoms; a tumor mass, not often found, owing partially to the smaller size of most of these tumors and also to the fact that the sigmoid is deeply situated and not easily palpated (rectal examination will reveal many of these tumors), and x-ray observations.

In the *differential diagnosis* the most common conditions that cause confusion are chronic ulcerative colitis, tuberculous colitis, diverticulitis, appendical abscess and functional diseases of the colon. These are probably best treated for a short time as functional cases, after which a careful reexamination should be made for persistence of the defects.

The importance of *physical methods of examination* in diseases of the abdomen, particularly of palpation in various positions, is stressed by V. I. Mirer and M. M. Langer (Novy khir. arkhiv. 33:76, 1935). Early resort to x-ray examination of the gastrointestinal tract and to exploratory operation are stressed. Colonic cancer may be operated on even in the advanced stage, because it grows slowly and is late in giving rise to distant metastases. **Resection of the involved segment** must be liberal, because of the fact that the colonic cancer extends not only locally, but likewise along the length of the intestinal wall. The authors recommend that in cancer of the cecum the entire right colon and the right third of the transverse colon, and in cancer of the sigmoid the entire left colon and the left third of the transverse colon be resected.

The subjective *symptoms* of colonic cancer may be grouped under the term "colic-like discomfort." Occult bleeding in the presence of colic-like discomfort constitutes a most suggestive sign of colonic cancer. In the neglected cases the cancer involves the peritoneum, spreads rapidly and gives rise to carcinomatous peritonitis.

Clinical experience favors the one-stage operation, extending its indications even in the presence of manifestations of acute ileus. The authors prefer the **side-to-side anastomosis**, 3 rows of intestinal suture, and covering the anastomosis with omentum or appendices epiploicæ. The abdomen is closed tight and posterior incision is added when drainage is indicated. In one-third of their cases, the growth extended into the retroperitoneal connective tissue. Their late results were quite encouraging. The presence of carcinomatosis of the peritoneum constitutes an absolute contraindication to the radical operation, while fixation of the growth constitutes a relative contraindication, **resection** being occasionally still possible in the latter.

**PATHOLOGY IN RELATION TO TREATMENT.**—The behavior of a growth in the colon depends not only on the histological character, but also on the soil. The family history in these cases is important, and there is without doubt a considerable tendency for the disease to run in families. Space will not permit discussion of the relationship between *adenoma* and *adenocarcinoma* in the colon, but there is good evidence to show that an adenocarcinoma frequently develops in an adenoma. It is also known that multiple adenomatosis of the colon runs in families, and that sooner or later the victims of this disease will develop one or more carcinomas and that these families tend to die out.

C. Gordon-Watson (Practitioner 126: 121 (Feb.) 1936) points out that it is a noticeable feature of colon growths that the large proliferative type, most frequently met with in the transverse colon, tends to be less malignant and less prone to invade the glands than the small scirrhous type, which ulcerates early, and is more prone to invade the glands; the latter, like the primary growths, are usually hard and small when involved. When, however, with a growth in the transverse colon there is malignant invasion of the glands, the *prognosis* is poor, because the superior mesenteric group around the aorta are frequently involved. Consequently, large growths with adhesions and without metastases should not be regarded unfavorably, but looked upon as evidence of good resistance. Prognosis must be considered good in this type of case if a satisfactory radical operation can be performed. In some instances large, soft glands are encountered in the proliferating or encephaloid type of growth, and it is important to note that these often prove to be inflammatory.

When, however, an adenocarcinoma is primarily colloid in character, the prospects of a cure are greatly diminished. In colloid cases growth is more rapid, the peritoneum is invaded early, and free fluid quickly forms. Metastasis spreads widely in the glands, which grow to a large size. If a growth is recognized as colloid in type, less risk to life should be taken, when considering the advisability of radical treatment, because prognosis is not good, even with ideal surgical procedures. In contrast to a primary colloid growth, mucoid degeneration in an adenocarcinoma is evidence of a low grade of malignancy. The histology of the primary colloid is distinct from mucoid degeneration and characterized by cells with large signet-like nuclei.

**SURGICAL TREATMENT.**—As stated above, there are few situations in the body where radical operation for carcinoma offers such promising results, especially in early cases. It is equally true that there are few surgical fields where judgment and experience play so important a part in relation to results. While it is true that in cases favorable for radical surgery the prognosis is good, meticulous care is required for radical surgery to be successful. The blood supply of the colon is not so good as that of the stomach; the contents of the colon are dangerously infective to the peritoneum, and gas distention after **resection** may be disastrous if there is no safety valve. The toxic state of the bowel behind a growth is a definite menace to aseptic surgery. Risks are far greater than in the case of gastric resection, and statistics from all sources show that the operative mortality rate for colon resections is high, whereas the ratio of recurrence is low, in comparison with gastric resections. In radical surgery for cancer of the colon and rectum the higher the “operability” rate, the higher the “mortality” rate and *vice versa*. If radical surgery is reserved for the freely mobile case, both the operative mortality rate and the ratio of recurrence will be low, and in estimating the value of statistics in these cases, the proportion treated by radical measures to those treated by palliative measures should be known. This is true for surgery of the rectum as well as for the colon. There can be no doubt that many cases of carcinoma of the colon which are adherent to the parietes, or to other viscera, can be mobilized and resected with good end-results in a high percentage of cases, a percentage which is necessarily lower than in freely mobile cases. Resections which deal with the proximal colon, where the contents are fluid, have a lower mortality rate than

with the distal colon, where the contents are solid. Every case with a growth in the distal colon is potentially obstructed.

*Preliminary Drainage.*—Drainage first spells “safety first.” It must be laid down as an axiom that preliminary drainage reduces the mortality rate of radical surgery to about one-half, and that in the absence of preliminary drainage, measures must be adopted at the time of resection to prevent postoperative distention, and if distention occurs, to avoid leakage at the anastomotic line, by means of a safety valve which will allow the escape of gas and fluid. It is universally agreed that *resection and anastomosis should never be performed in the presence of acute or subacute obstruction*, and that a preliminary **cecostomy** or **colostomy** is usually the wise course to adopt. Opinions differ as to the respective merits of a so-called “blind” cecostomy (*i. e.*, a cecostomy performed without exploration of the abdominal cavity and often under local anaesthesia) and an **exploratory laparotomy** to locate the seat of obstruction followed by a **cecostomy** or in some cases **colostomy**. The main argument against a “blind” cecostomy is the possibility of a mistake in diagnosis. The strongest argument in its favor is that the mortality of the operation, in acute cases, is definitely lower than it is for the exploratory method. It is important to note that left-sided obstruction is not always relieved by cecostomy.

When *obstruction is subacute*, the case for “blind” cecostomy is not so strong. In some of these a freely mobile growth can be safely **marsupialized** and the **colon drained** by the method of Paul, or some variant of Paul’s operation, though it is doubtful if the end-results of cases treated by this type of operation can be compared with planned resections in the quiescent period. It may not always be possible to remove the

mesentery as freely as is desired in a Paul’s operation, and the resulting anastomosis will not have that freedom in the abdominal cavity which is desirable and can often be secured by resection in the quiescent period.

*Results.*—The results obtained in 116 cases of carcinoma of the colon at the Malmo General Hospital between 1917 and 1931 are given by F. Koch (Arch. f. klin. Chir. 184:39 (Nov. 18) 1935). Palpation of the tumor was possible in 48 per cent. of the cases while the correctness of the x-ray diagnosis was established in 75 per cent. Operation was possible in only 40 per cent. of the cases. Primary resection was favored as the operation of choice and was carried out in 42 cases. The immediate mortality was 16.6 per cent. Acute obstruction complicated 32.7 per cent. of the 116 cases. A follow-up study established that 66 per cent. of the cases in which radical operation was performed were free from recurrence after 5 years.

In a report from Johns Hopkins Hospital by T. S. Raiford (Ann. Surg. 101:863, 1935) concerning 192 cases of cancer of the colon and 319 cases of cancer of the rectum since 1889, he shows that 53 per cent. of the patients entering the hospital with carcinoma of the rectum were inoperable. Of those subjected to resection, 22.2 per cent. died from the effects of the operation. Of those surviving the operation, 60.9 per cent. died of recurrence, and 39.1 per cent. were presumably cured.

*Technic in Surgery of Colon.*—The complex and the complicated in surgery of the large intestine is discussed by G. Gordon-Taylor (Proc. Roy. Soc. Med. 29:343 (Feb.) 1936). The author calls attention to anatomicopathological conditions of the large intestine and their bearing on operative surgery. A neoplasm of the large intestine may be complicated by other conditions. Surgical

interference for disease of the gall-bladder may result in the discovery of an unsuspected carcinoma of the large intestine. Pain in the right iliac fossa in middle age or later life always should awaken the suspicion that a constricting carcinoma of the distal part of the colon is present. The surgeon may first come in contact with a neoplasm of the colon when a carcinomatous ulcer or a stercoral ulcer above the stricture undergoes perforation. When extraperitoneal leakage occurs, a localized abscess which may be formed may be opened and the growth satisfactorily excised subsequently.

Volvulus of a segment of large intestine containing a growth may demand operation because of the urgency of the symptoms. An invaginated growth may present at the anal orifice or, by producing acute abdominal enlargement, may give the first evidence that a colonic tumor is present. A pelvic tumor may prove to be a Krukenberg tumor. Hydrocele that develops suddenly may prove to be of tuberculous or neoplastic origin.

*Anatomical abnormality may complicate otherwise apparently simple operations.* The left portion of the colon may cling to the midline and have a short mesocolon. The transverse colon may be concealed by a distended small bowel. The embryonic midgut may have failed to rotate. The right side of the colon may be extended above the liver to the diaphragm. More infrequently the colon may be in the thorax.

The gravity of **intestinal resection** and **anastomosis** will be influenced to a degree by the number of lines of surgical suture, but the *operative prognosis* is dependent upon a number of factors. The author believes that in complicated or plurisegmental removal of the bowel for cancer the immediate risk to life is not greatly increased by radical operation. Cases in which plurisegmental resection is performed for cancer of the

large bowel may be divided into the following 5 groups: (1) those in which involvement of the abdominal wall is marked; (2) those in which the growth has infiltrated other portions of the alimentary tube; (3) those in which some additional segment of the alimentary canal other than the bowel is involved in the growth; (4) those in which a solid viscus, or a hollow viscus unconnected with the alimentary canal, is involved by the growth; and (5) those in which multiple resection is necessary because of some complicating, accidental, or concomitant condition unconnected with the primary neoplasm. The author believes that the debatable point is the prospect of prolonged survival rather than immediate risk to life.

Pelvic infection may necessitate resection of the large intestine. Nontuberculous granuloma appears to be especially frequent in the cecum and is readily mistaken for tuberculosis. Certain forms of acute intestinal obstruction may demand double resection of the bowel, one of the segments being colonic. Survival from multiple resection of the bowel for gunshot injury is rare. For cure, anastomotic ulcers consequent on gastro-jejunosomy demand resection of the stomach and jejunum and perhaps also of the colon. Resected intestine with its mesenteric attachments left intact may be used to construct a vagina or to replace segments after resection, as in cases of diverticulitis. The author has encountered only 1 case of gangrene of the large bowel attributable to mesenteric occlusion.

A complex and complicated technic requiring from 2 to 5 operations for the removal of a cancerous segment of colon is defended. Grey Turner admits an operative mortality of 12 per cent., while holding that ultimately it may be reduced to 5 per cent. In resecting a segment of the distal part of the colon, the

author establishes a prophylactic cecal anus. For many *growths in the distal part of the colon, diverticulitis, volvulus and megacolon*, he is using the **exteriorization method of Paul-Mikulicz** more and more frequently. In 84 cases in which he performed a simple colectomy by this technic the mortality was only 2.4 per cent. An operation in one stage is safe in many cases of cancer of the right side of the colon, especially if

even though in 1891 Councilman and Lafleur, in their extensive and complete clinical and pathological investigations, definitely showed the amebæ could produce solitary and multiple liver abscesses, it was not until Sir Leonard Rogers in 1902 established that solitary "tropical" abscess was invariably the result of amebic infection. In a consideration of liver abscess, it is important from a prognostic and therapeutic standpoint to

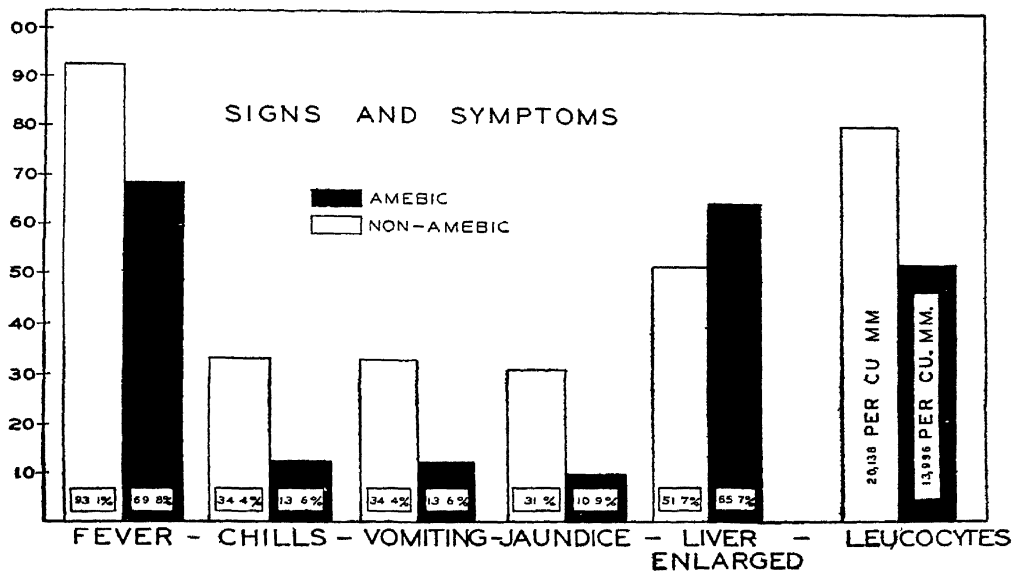


Fig. 3.—Graphic representation of incidence of various clinical manifestations both in amebic and nonamebic abscesses of liver. (Ochsner and DeBakey: Am. J. Surg.)

enterostomy is performed above the anastomosis and a catheter is inserted. For other cases, some type of exclusion operation in two stages is advocated. In cases of *chronic ulcerative colitis* the **Coffey operation** replaces a dangerous one-stage operation by a safe three-stage intervention. The author concludes that radical, complex, multiple resections often repay the enterprising surgeon in dealing with cancer of the colon.

#### LIVER.—AMEBIC ABSCESS.—

Up to the beginning of the present century, relatively little was known concerning the etiology of solitary abscesses. A. Ochsner and M. DeBakey (Am. J. Surg. 29:173 (Aug.) 1935) state that

differentiate amebic from pyogenic abscesses. A rational consideration of liver abscess is not possible unless this differentiation is made. Such differentiation is imperative, because in amebic hepatic abscess the prognosis is good and the treatment relatively simple, whereas in pyogenic abscess the prognosis is extremely grave and the treatment more difficult.

The authors have made a study of 73 cases of *amebic abscesses* of the liver. They found the average age was 44 years. The ratio of males to females was 8 to 1.

A history of an antecedent diarrhea was given in 59.6 per cent.; 17.4 per cent. showed amebæ in the abscess, and

36.1 per cent. showed amebæ in the stool in those cases in which these examinations were performed.

The principal symptoms and signs were pain and tenderness, being found in 79.4 per cent. Fever and enlargement of the liver were found in 69.8 and 65.7 per cent., respectively. A diagnosis of amebic hepatitis was made preoperatively in 68.4 per cent. Positive x-ray diagnoses were made in 87.7 per cent.

The *prognosis* in amebic hepatitis depends largely upon the presence of secondary infection and the type of operation used. In a series of 4035 cases collected from the literature, and including the authors' own cases, in which open operation was used, 1908 (47.2 per cent.) ended fatally. In a similar series of 459 treated conservatively there were 32 deaths, a mortality rate of 69.9 per cent.

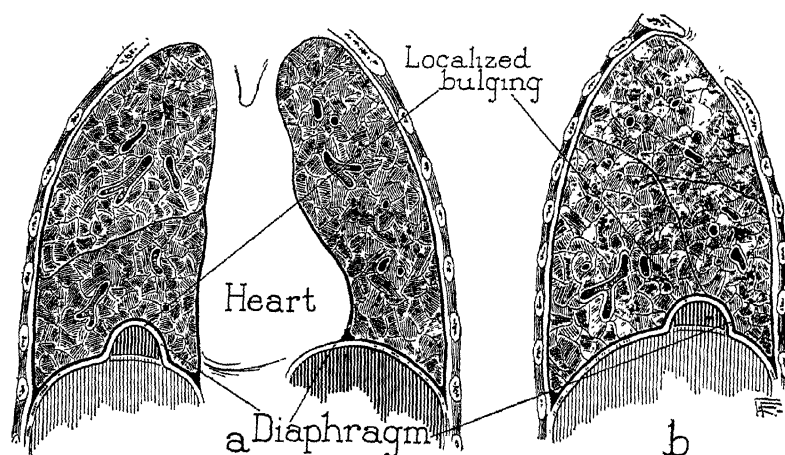


Fig. 4.—Diagrammatic drawing showing bulging upward into lower lung field of a localized hepatic abscess. In anterior-posterior roentgenogram (a) bulging is in medial portion of lung field, whereas in lateral roentgenogram (b) it is located more anteriorly than posteriorly. (Ochsner and De Bakey: Am. J. Surg.)

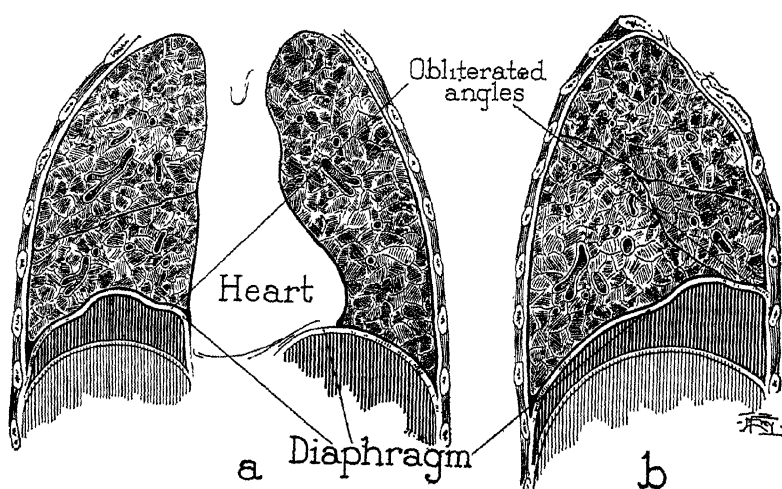


Fig. 5.—Diagrammatic drawing showing characteristic elevation of diaphragm in subphrenic abscess following rupture of hepatic abscess. In anterior-posterior roentgenogram (a) there is obliteration of cardiophrenic angle, costophrenic angle being uninvolved. In lateral roentgenogram (b) there is an obliteration of anterior costophrenic angle, posterior costophrenic angle being free. (Ochsner and De Bakey: Am. J. Surg.)



In the authors' series of 70 cases in which treatment was used, 10 succumbed, a mortality of 14.2 per cent. Forty-six were operated upon with 9 deaths, a mortality rate of 19.5 per cent. Of these, 16 were operated upon, employing the transpleural approach, with 4 deaths, a mortality rate of 25 per cent. Fourteen were operated upon through a right rectus incision with a 21.4 per cent. mortality rate. Seven had simple

(May) 1936) report in considerable detail a case of amebic abscess of the liver which was treated by **multiple aspirations** and the simultaneous injection of **emetine** intramuscularly and into the abscess cavity.

*Case History.*—The patient was a man 52 years of age who was admitted to the hospital with a 2 months' history of pain in the lower right side, swelling in the right upper quadrant of the abdomen, diarrhea, and blood in the stools. Examination revealed a friction

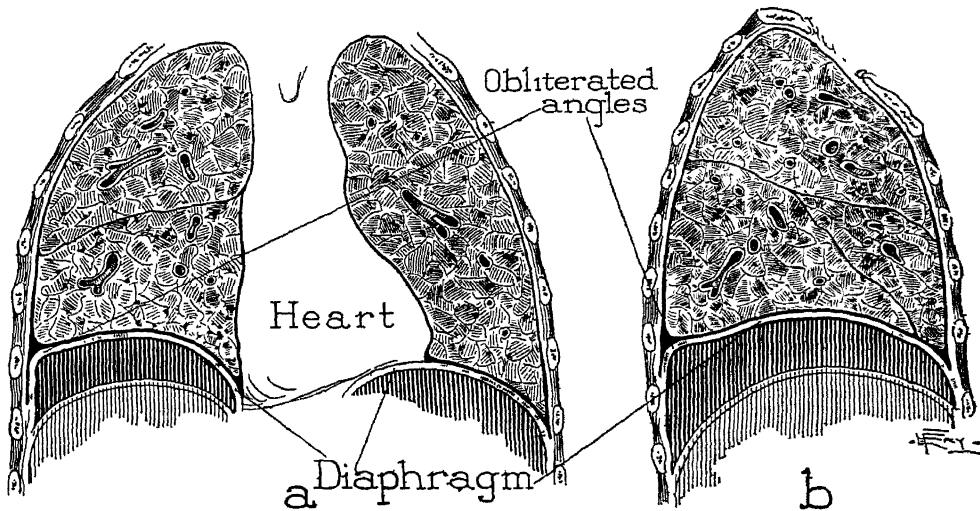


Fig. 6.—Diagrammatic drawing showing changes in roentgenogram obtained in subphrenic abscesses resulting from intraabdominal infection aside from liver abscess. In anterior-posterior roentgenogram (a) there is obliteration of costophrenic angle, whereas in lateral roentgenogram (b) there is an obliteration of posterior costophrenic angle. (Ochsner and DeBakey: *Am. J. Surg.*)

incision and drainage over a presenting mass, with a 14.2 per cent. mortality rate. Nine had retroperitoneal operations with an 11.1 per cent. mortality.

The lowest mortality rate (4.1 per cent.) was obtained in 24 cases treated conservatively by aspiration and the use of amebicides.

The *treatment* of amebic hepatic abscesses which are not secondarily infected consists of **aspiration** and the use of **amebicides** and **open operation** should be employed only in those cases in which there is infection with pyogenic microorganisms.

H. A. Royster, H. B. Haywood and W. W. Stanfield (*Ann. Surg.* 103:794

rub over the right sixth interspace anteriorly and a tense swelling in the right upper quadrant of the abdomen. The liver was enlarged upward to the third rib and downward to a point 3 inches below the costal arch. The temperature was 103° F. (39.4° C.) and the leukocyte count 18,000. The protozoa of *endameba histolytica* were found in the stools. X-ray examination confirmed the clinical diagnosis of abscess of the liver.

The treatment consisted of multiple aspirations of the liver abscess through the midline and the simultaneous injection of emetine both intramuscularly and into the abscess cavity.

During his convalescence the patient developed pleurisy with effusion on the right side. Seven liver aspirations were performed. The patient was discharged completely well approximately 6 weeks after his admission to the hospital.

In discussing the literature the authors state that aspiration has been performed previously as a curative measure, and that emetine injected intramuscularly is a specific against the disease. They have given intramuscularly 1 grain (0.065 Gm.) of emetine daily for 10 days.

**NONPARASITIC CYSTS OF LIVER.**—Solitary nonparasitic cysts of the liver are rare. Fewer than 100 cases have been reported. C. Lenormant and

of her diet and sent to a watering place for two seasons. During the second season the tumor developed. Examination on her admission to the hospital disclosed a tumor of the liver. Operation by marsupialization was followed by uneventful recovery.

The majority of nonparasitic cysts of the liver are *cystadenomas* with an epithelial lining which is generally made up of a single row of high cylindrical or

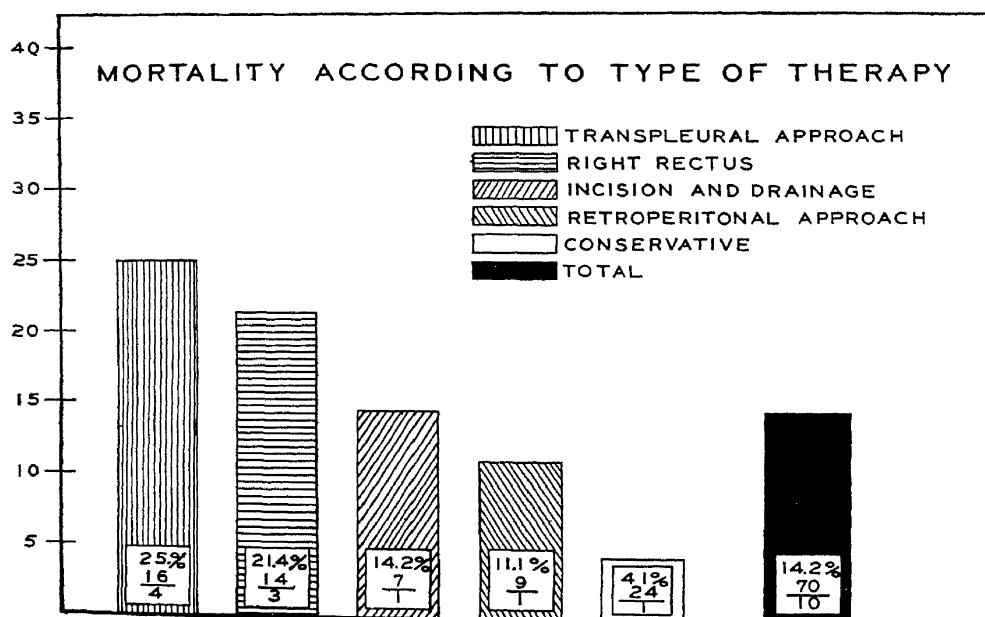


Fig. 7.—Graphic representation of mortality rate obtained in present series by various types of therapy. (Ochsner and De Bakey: Am. J. Surg.)

J. Calvet (J. de chir. 45:715 (May) 1935) present a tabular summary of 66 cases collected from the literature, refer in addition to 25 cases reported without detail by Mayo and Harrington, and bring up to date, the bibliography published in the Annals of Surgery by Jones in 1923.

They then report a case of their own, that of a woman 46 years old who entered the hospital with an epigastric tumor. The patient had been well up until 2 years previously, when she began to have digestive disturbance and epigastric pain not related to the taking of food. She was treated by regulation

cubical cells very similar to those of the epithelium of the hepatic ducts. Sometimes the epithelium is flattened and polyhedral, particularly in large cysts in which it seems to have been affected by intracystic pressure. These cysts are benign tumors originating from abnormal proliferation of the intrahepatic bile ducts. There are no very characteristic clinical symptoms except pain and the tumor itself, which may be quite large and often fluctuating. The biological reactions for echinococcus cyst are negative. The tumor increases in size slowly and progressively. Like other gland cysts, it may be complicated by

hemorrhage, rupture, torsion, or compression. It may simulate various other abdominal conditions. Even after the diagnosis of liver cyst has been made and operation has been begun, it is necessary to rule out cysts due to dilatation of the extrahepatic bile ducts, lymphatic and blood cysts, and dermoid cysts, which are much rarer.

The preferable *treatment* is total **excision** if there is a line of cleavage between the cyst and the liver parenchyma. If there is no line of cleavage and it is necessary to incise the liver parenchyma, the operation is difficult technically and there is danger of serious hemorrhage. Under such conditions **marsupialization** is to be preferred.

**SUBPHRENIC ABSCESS.**—R. L. Masciottra and R. V. Chilese (Rev. med. quir. de patol. fem 3: 519, 1935) present a systematic and comprehensive discussion of subphrenic abscesses, a review of the recent literature, and complete reports of 7 cases. The classification which the authors consider the most practical is: suprahepatic abscesses (right and left); subhepatic (anterior, posterior, or in the lesser peritoneal cavity); and retroperitoneal abscesses. They believe that a serous pleural exudate is a usual accompaniment of subphrenic abscesses even in an early stage and does not necessarily imply a late diagnosis. They regard the induction of pneumoperitoneum for *diagnosis* as unjustifiable, but discuss at length the importance of x-ray examination for diagnosis and the injection of lipiodol after evacuation of the abscess for study of the relationships of the cavity. They emphasize particularly the finding of bile mixed with the pus since, as judged from the literature, this feature has been neglected and the study of biliary peritonitis and pyobiliary abscesses is still undeveloped. For right and left superior and inferior subdiaphragmatic abscesses they have

found **Ochsner's anterior extraperitoneal approach** to be best.

As all of the cases they report were those of women, the incidence of hepatic and biliary lesions was unusually high as compared with that of gastrointestinal lesions. In 2 cases the subphrenic abscess was the result of cholecystitis and in 1 case each, of multiple suppurating hydatid cysts of the liver, appendicitis, and perforated gastric ulcer. In 5 cases the abscess followed an operation. The interval between the operation and the appearance of the symptoms varied from 5 to 35 days. Two of the abscesses were right superior, 3 were subhepatic, and 1 was retroperitoneal. In 1 case a right and left superior abscess were found. There were 3 deaths.

**CIRRHOSIS OF LIVER.**—A discussion of cirrhosis of the liver by E. C. Henrikson (Arch. Surg. 32: 413 (Mar.) 1936) is given according to the classification of Bell: (1) portal cirrhosis, (2) obstructive biliary cirrhosis, (3) pigmentary cirrhosis, and (4) syphilitic cirrhosis.

**Etiology.**—The etiology of cirrhosis is obscure. Alcohol is now regarded as of less importance as a cause than it was formerly believed to be, but the evidence presented by the statistics showing a sharp decline in the number of cases of cirrhosis diagnosed after prohibition suggests that there is some relationship between its use and the occurrence of portal cirrhosis. Among other causative agents taken into the gastrointestinal tract are spices, chloroform, arsenic, and copper. The hypothesis that portal cirrhosis is due to toxins brought to the liver by the portal system seems to be supported by experimental and clinical observations.

**Symptoms and Diagnosis.**—In the diagnosis of cirrhosis of the liver, cardiac and renal pathological conditions must be ruled out. The most common symp-

toms are referable to the gastro-intestinal tract. Of 162 cases, such symptoms occurred in 126. They include abdominal pain or discomfort, nausea, vomiting, constipation, diarrhea, anorexia, hematemesis, and melena. Other common symptoms are weakness, malaise, edema, dyspnea, jaundice and nocturia. The most common physical finding is ascites. This was present in 121 of the 162 cases cited. The next most frequent sign is a palpable liver. Frequently there is a cardiac murmur and albumin, and casts are found in the urine. The most common cause of death is hepatic insufficiency, which often leads to coma before death.

**Treatment.**—The best results from medical management are obtained by adherence to a rigid dietary régime. There is good experimental and clinical evidence to show that a high carbohydrate diet protects the liver and combats hepatic insufficiency. The diet should exclude alcohol, eggs, spices, condiments, and fats. Dehydration by catharsis, limitation of the fluid intake and diuresis helps to combat the ascites and edema. In the author's cases treated only by medical management, the length of life after the onset of ascites was 16 months.

When surgical intervention is considered, the patients must be carefully selected. According to Talma, operation is contraindicated in the presence of: (1) a high-grade disturbance of the function of the liver, (2) icterus, (3) xanthoma, and (4) pruritis. If the patient is a poor surgical risk, paracentesis may be the only procedure possible. Other methods of draining the ascitic fluid, such as Ruotte's saphenoperitoneal anastomosis, Handley's femoral canal drainage, and the use of collar-button-like tubes for subcutaneous drainage, are said by many to give good results in some cases. Operations to establish collateral circulation, such

as the **Talma-Morison omentopexy** or some modification of it, also give good results in selected cases. The more formidable procedures for establishing a shortcircuit to relieve the liver of some of the blood entering from the portal system, such as the formation of an **eck fistula** or **anastomosis of the superior mesenteric vein and the inferior vena cava**, should be used only for especially selected and well-prepared patients.

Of Henrikson's series of 19 patients operated upon for cirrhosis, 67 per cent. died within 1 year after the operation. Of 31 patients with cirrhosis subjected to operations of another type, 77.4 per cent. died within 1 year. In Henrikson's cases the average duration of life after operation was 5 months, whereas in cases treated medically it was 18.3 months.

A study of 22 adequately followed cases of portal cirrhosis of the liver with ascites, which were treated by **omentopexy** is outlined by R. S. Grinnell (Ann. Surg. 101:891 (Mar.) 1935). Fifteen of the patients were males. The youngest patient was 12 years old and the oldest 68 years. The average age was 41 years. The average duration of symptoms before the operation was 11 months. Forty-three per cent. of patients gave a history of alcoholic excess. Jaundice was present in only 21 per cent. and was mild. Ascites was present in every case. Its average duration before the operation was 6 months. The operation performed was either the **Schiassi modification of the Talma-Morison technic** with suture of the omentum to the parietal peritoneum or some other variation in which the omentum was placed in the properitoneal tissues or in or between the split rectus muscle fibers.

Six (27 per cent.) of the patients died within 11 days after the operation. Of the remaining 16 cases, 12 died later, 2

(9 per cent.) are living, and 2 could not be traced after a year. The two who are still living are free from symptoms after 5 and 17 years, respectively. Seven (32 per cent.) of the patients, who were classed as benefited, survived the operation for  $\frac{1}{2}$  to  $10\frac{1}{2}$  years. Thirteen (59 per cent.) were not benefited. Six of the latter died soon after the operation. The remaining 7 showed a progressive course uninfluenced by the operation and died after from 3 weeks to 6 months.

The 2 patients who are still alive and free from symptoms and 2 who were benefited showed evidence of a collateral portal circulation at the time of the operation, a finding which the author regards of prognostic value. The average age of the 2 patients who are still alive and free from symptoms and of the 1 benefited patient who survived for 10 years was 9 years less than that of the entire group and 15 years less than that of the group who were not benefited.

The author believes it probable that **omentopexy** would prove of greater value if it were performed earlier, before liver injury becomes severe and if it were done even before the development of ascites in cases with hematemesis is evidence of an established collateral circulation. If it is accompanied by **ligation of the coronary vein and vasa brevia** and possibly in certain cases by **splenectomy**, which reduces the flow of blood through the portal vein by more than 20 per cent., the danger of hemorrhage may be lessened.

**Splenectomy** in treatment of *varicose hemorrhages* in cirrhosis of the liver is discussed by E. Mandel and G. H. Marcus (Ztschr. f. klin. Med. 128: 504 (Sept. 12) 1935). The authors point out that hemorrhages from varices in the stomach and esophagus, which develop after circulatory disturbances in the region of the portal vein, have been

treated with extirpation of the spleen. Such varices develop in circumscribed and in general stasis. They represent the collateral channels of the portal vein. Thus, they are always present in cases of thrombosis of the splenic vein in which splenectomy was done with good results. Splenectomy has been recommended also for the varices that develop in the course of cirrhosis of the liver. If it is assumed that the development of varices in cirrhosis of the liver is at least partly caused by the chronic generalized stasis of the portal vein, it seems natural to assume that an eventual favorable effect of splenectomy is to be found in hemodynamic factors like those that exist in thrombosis of the splenic vein, *i. e.*, in a localized stasis. However, an influence on the varices of the stomach and of the esophagus is conceivable only if there exist connections between the splenic vein and the varices of the esophagus and stomach. For this reason the authors decided to study the anatomy of this venous region. After mentioning the connections that normally exist between the esophageal veins and the splenic vein, they point out that these anastomoses, which normally are extremely fine, become dilated and tortuous when they become collaterals in case of cirrhosis. They describe their observations in 4 cases of cirrhosis of the liver. Then they point out that, in addition to the clarification of the anatomic conditions, the direction of the blood currents in this venous region is important. They are convinced that the currents in this region are dependent on many different pressure fluctuations, the more so since the branches of the portal vein are without valves. If the flow through the liver is inhibited by a cirrhotic process, the splenic blood passes through the collateral channels in the region of the stomach and the esophagus. Thus, if splenec-

tomy is done, a large portion of the blood that passes through the varices is eliminated, and the veins of the mucous membrane are relieved of some of their load. Moreover, it is possible that the removal of the spleen changes the pressure conditions in the splenic vein and its collaterals in such a manner that blood from gastrointestinal veins, which normally would enter the portal vein, passes by way of the stump of the lienal vein and its anastomoses into the region of the cava inferior. The authors were able to demonstrate such connections in all cases. Theoretical reasoning permits the conclusion that splenectomy reduces the load of the varices and thus also the danger of hemorrhage.

**MESENTERY.—PRIMARY RETROPERITONEAL AND MESENTERIC TUMORS.**—C. C. Fleischer-Hansen (Nord. med. Tidskr. 9:608 (Apr. 20) 1935) reports 7 cases of primary retroperitoneal and mesenteric tumors and considers that they belong to the same group. The tumors are chiefly solid or cystic. In the mesentery, cystic tumors are 3 or 4 times as common as solid tumors. Of the solid retroperitoneal tumors, 40 per cent. are lipomas and 40 per cent. are edematous, fibromatous, or myxomatous neoplasms. The group includes also bone and cartilage tumors, sarcomas, and neuromas. The lipomas grow to a large size and may exert pressure on neighboring organs. The solid and cystic tumors occur much more frequently in women than in men. The histologically malignant tumors rarely metastasize. In children, however, rapidly-growing, typically-malignant lymphosarcomas occur and metastasize rapidly. The cystic tumors lie most commonly in the mesentery of the ileum, but may be found also in the mesentery of the jejunum and transverse colon. As a rule, they are

chylous cysts, and more rarely polycystic lymphangiomas.

**SYMPTOMS.**—As long as the neoplasms are small, symptoms may be absent. Larger tumors may cause only vague symptoms, such as headache, lassitude, and insomnia. The largest tumors produce a sense of fullness, weight, and pressure in the abdomen. The mesenteric tumors usually produce pain, obstipation, dyspepsia, emaciation, weakness, and lassitude. Ileus seems to occur more often with cystic tumors than with solid type.

**MULTIPLE CYSTS.**—A. Bonaccorsi (Policlinico (sez. chir.) 42:685 (Dec.) 1935) reports a case, in a 6-year-old girl, of voluminous cysts of the mesentery of lymphatic origin. One of the cysts contained a bloody fluid and the two others a simple chylous fluid. About 500 cases have been recorded in the literature. The development of the symptoms in this case suggested the common sequence of acute appendicitis followed by rupture of the appendix and the formation of a local periappendiceal abscess. However, the tumor mass persisted and there was only a slight elevation of temperature. The syndrome presented is explained by the hemorrhage into the cyst and compression of the lumen of the small intestine. At operation in this case a large cyst was found in the mesentery of the small intestine. It was removed with resection of the adjacent portion of the small intestine.

**MESENTERIUM COMMUNE.**—From a study of his cases A. Runco (Radiol. med. 22:147 (Feb.) 1935) concludes that this condition is due to arrest of development of the intestine at about the tenth week, before the umbilical loop has begun to rotate around the axis formed by the superior mesenteric artery.

**Symptoms.**—The condition may be asymptomatic for a long time, but

sooner or later gastrointestinal disturbances are apt to develop resembling the dyspeptic disturbances associated with marked vagal hypertonia. Complications due to hypermobility of the intestines are rare, but are apt to be serious.

**Diagnosis.**—The diagnosis is difficult, requiring a very careful x-ray examination of the entire gastrointestinal tract. This should be made with a barium meal and enema and with the patient in the upright, recumbent, and possibly the Trendelenburg position, in order that any organic lesion, stenosis, or occlusion may be promptly detected.

**RETRACTILE MESENTERITIS IN "COMMON MESENTERY."**—C. Uggeri (Arch. ital. d. mal. d. app. diger. 5:183, 1936) reports a case in an unmarried woman 23 years of age. At the age of 18, she complained of digestive disturbances with constipation. Three years later, the patient suffered an acute abdominal attack for which appendectomy was done. The abdominal disturbances continued, with increasing constipation, no bowel movements occurring without a purge or enema. Occasionally, there was an increase in abdominal pain with borborygmi and swelling of the abdomen. X-ray examination showed that the second and third portions of the duodenum turned to the right instead of to the left. The entire jejunum and ileum were situated along the flank and in the right iliac fossa. The colon was situated entirely in the left side of the abdominal cavity. The cecum was in a median position and low, fixed to the hollow of the sacrum. The transverse colon was folded along the left flank, and the descending colon was next to the cecum. At operation an **ileosigmoidostomy** was done. Of particular interest was the presence, in the ascending segment, of a mesocecum, which presented all the signs of mesenteritis.

## MESENTERIC INFARCTS.—

**Etiology.**—A. Ameline and C. Lefebvre (J. de chir. 46:481 (Oct.) 1935) believe that mesenteric infarcts are due, as a rule, to the occlusion of a mesenteric artery or vein or both. The local factors may be subdivided into mechanical processes, such as abdominal trauma; the presence of foreign bodies; functional pathological processes, such as gastralgia, constipation, and diarrhea; and organic pathological processes, such as gastroduodenal ulcers; infections, such as those of dysentery, typhoid fever, appendicitis, and parasitic infections; tumors of the digestive tract; cirrhosis of the liver; cholecystitis; cholelithiasis; splenomegaly; pancreatitis; salpingo-oophoritis; uterine fibromyoma; ovarian cysts; carcinoma of the cervix; and renal lesions, which are usually associated with cardiac or vascular disturbances, forcible dilatation of urethral strictures, suppurative orchitis, and prostatitis.

Included in the general causes are disturbances of the circulatory system, especially arteriosclerosis, specific and nonspecific arteritis, Buerger's disease, and venous thrombosis, purpura and hemophilia. Mesenteric infarcts have occurred in anaphylactic shock; focal and general infections; intestinal infections; in diabetes, obesity, lead poisoning, alcoholism, morphine addiction; in the excessive use of tobacco; in nervous disturbances; and endocrine disorders, such as thyrotoxicosis and adrenal tumors.

**Symptoms.**—The onset is sudden, with severe pain, which is localized mainly in the right iliac fossa and the umbilical and epigastric regions. Vomiting and a serosanguinous diarrhea follow. The condition is most often confused with peritonitis and acute appendicitis.

**Treatment.**—The treatment is surgical and depends upon the extent and degree of the lesion. Drugs having a vasodilating and antispasmodic action and combatting shock may be found beneficial. The mortality in the author's cases was 73.55 per cent.

**MESENTERIC EMBOLISM.**—N. S. Okun (Vestnik khir. 43:240 1936) reports 11 cases of embolism of the superior mesenteric artery. In 8 cases the condition was not diagnosed before operation or necropsy.

**Etiology.**—In 9 cases the factors were acute, recurring, ulcerative, vegetative, and chronic endocarditis and atheromatosis of the aorta.

**Symptoms.**—Three of the author's cases were characterized by diarrhea; 3 presented a picture of intestinal obstruction; in 1 there were symptoms of both diarrhea and ileus; while the remainder presented a vague symptomatology.

**Diagnosis.**—This is difficult, the presence of pathologic alterations in the cardiovascular system constitutes an aid.

**Treatment.**—Early operation, with resection of the involved intestine, is indicated. All of the author's cases died.

**MESENTERIC VASCULAR OCCLUSION.**—**Etiology.**—H. Sneierson (Ann. Surg. 102:171 (Aug.) 1935) recognizes 4 main causes: (1) trauma, (2) external pressure, (3) embolism and thrombosis, and (4) inflammatory or degenerative occlusion of the lumina. The most common of these are thrombosis and embolism. The most important causes of arterial occlusion are endocarditis and arteriosclerosis. Recently thromboangiitis obliterans has been reported as an important factor. The superior mesenteric artery is the site of the greatest number of the lesions, probably because it is larger than the inferior, arises above the latter,

and is almost parallel with the aorta. J. Douglas (*Ibid.* 102:636 (Oct.) 1935) recognizes as etiological factors arteriosclerosis, atheroma, cardiac disease, aneurism, abdominal trauma, a history of phlebitis or polycythemia, or chronic sepsis.

**Pathology.**—Gangrene of the bowel occurs in spite of an apparently profuse blood supply, probably because of the anemia produced by the violent spasmodic contraction of the intestine set up by acute blockage of an artery. When an arterial occlusion is slight or occurs gradually, the area affected is supplied by the arteries above and below. In venous occlusion, the hemorrhagic infarction is due to the fact that the blood has no outlet and there is retrograde thrombosis of the arteries. The part of the intestine affected is thickened, dark red to black, and soon becomes gangrenous. The lumen contains thick, tarry blood. The bowel wall is gorged with blood, and the mucosa may be ulcerated. The serous coat may be covered by an inflammatory exudate, and the peritoneum contains bloody fluid. There may be a general peritonitis. In Larson's series of 36 autopsies made at the Mayo Clinic, a vascular occlusion was noted in every case. In only 2 of Douglas' 11 patients was a thrombosis of the mesenteric vessels discovered.

Although there was gross damage to the intestinal wall, it was suggested that in a certain number of cases the infarction began in the smaller vessels, either close to, or in, the vessel wall and in some instances was perhaps due to an anærobic infection originating in the intestine.

**Symptoms and Signs.**—The symptoms and signs are those of intestinal obstruction and peritonitis. Recognition of the etiological factors, as mentioned above, might suggest that in the pres-



ence of acute abdominal symptoms mesenteric occlusion was the causative factor. When the signs pointing to an acute abdominal catastrophe are a high leukocyte count with acute abdominal pain, a previous history of thrombosis or a source of embolism, an early subnormal temperature, abdominal rigidity, and melena, there is a definite group pointing to mesenteric occlusion. However, Trotter reported that a preoperative diagnosis was made in only 13 of 360 cases which he reviewed. Sneierson records 8 cases in the past 10 years in which there was 1 recovery.

**Treatment.**—Douglas (*Ibid.*) advises not only **early operation**, but **immediate resection** and **anastomosis**, rather than an ileostomy or exteriorization.

**MESENTERIC THROMBOSIS.**—J. K. Donaldson and B. F. Stout (*Am. J. Surg.* 29:208 (Aug.) 1935) discuss the venous type. Since the mesenteric thrombosis may occur as a complication of various conditions, the picture may be complicated by various pathologic elements. A striking *symptom* is the disproportion of the abdominal tenderness and the duration of symptoms to the abdominal rigidity. The abdomen is usually widely and definitely tender to deep palpation and the abdominal rigidity is not nearly as marked when the possible duration of the complaint and the definite tenderness are considered. The normal leukocyte relationship is moderately disturbed in the early stages, but is markedly distorted later. A palpable mass may or may not be felt. Occult blood is uniformly present in the stool and bowel movements continue, dark and soft to liquid in nature. Coffee-ground-like vomitus may supervene. The temperature in the uncomplicated picture is low.

*Differential diagnosis* is made from intestinal obstruction, appendicitis, peritonitis, peptic ulcer, lead colic, simple

enteritis, cholecystitis, gastritis and typhoid fever. Arterial thrombosis is much more rapidly fatal than the venous type, which is probably compatible with recovery without surgery in a certain percentage of cases.

**OMENTUM.—Function.**—In experimental investigations on the function of the great omentum by H. Ueda and W. Mabuchi (*Deutsche Ztschr. f. Chir.* 245:390, 1935), the liver, kidneys, spleen, mesenteric glands, and stomach of rabbits were examined at various intervals after extirpation of the omentum. Soon after operation, cloudy swelling, degenerative fatty infiltration, and loss of glycogen occurred in the hepatic cells. In 18 of 66 rabbits localized or diffuse necrosis was found in the hepatic parenchyma. Twenty days after the operation an enlargement of the Kupffer star cells, even localized nodular proliferations, and also, masses of cells in Glisson's capsule were observed. From the thirtieth day after operation the glycogen content of the hepatic cells gradually increased. In the kidneys, hyperemia and degenerative changes of the epithelium were noted. In 9 of 44 animals, interstitial hemorrhages occurred. In the spleen, infiltration of the splenic pulp and lymph follicles were noted. The mesenteric glands showed lymph sinus catarrh and, finally, enlargement and proliferation of the histiocytic cells with phagocytosis of the brown pigment granules. In 6 of 44 animals ulceration of the stomach was found. In 14 there were ulcers of the mucous membrane. In 20 days, cystic dilatation of the gastric glands and proliferation of the propria were observed. The injection of typhoid bacillus toxin killed 12 of 17 rabbits deprived of the omentum.

The studies on iron metabolism showed that 4 days after the operation

an iron reaction appeared in the stellate cells of the liver, the histiocytic cells of the lungs, and the lymph glands. In the cells of the lungs and the lymph glands the reaction increased up to the fourteenth day and then disappeared. In the stellate cells in the liver it was most intense after 20 days and then weakened up to the seventy-fifth day. It was much stronger on the spleens of the animals deprived of the great omentum than in the spleens of the normal animals. It was demonstrable in Bowman's capsule of the kidneys and in the uriniferous tubules from the first day, but after 30 days it was weak.

There was a decrease in erythrocytes and hemoglobin in the blood within 17 days, and after 3 to 14 days the leukocytes decreased. The eosinophiles disappeared. The viscosity of the blood was lowered. The erythrocyte sedimentation rate was accelerated for 14 days after the operation, and then became slower. The resistance of the erythrocytes to hypotonic sodium chloride solutions was strengthened for from 3 to 14 days. There was a decrease in precipitin formation.

They found that extirpation of the omentum has a marked effect on the carbohydrate metabolism. The changes perhaps depend less upon the removal of the omentum than upon the temporary postoperative dysfunction of the reticulo-endothelial system and especially the resulting changes in the liver. The total protein content showed a tendency to increase. The blood cholesterin showed a great increase, becoming normal in one month.

The total fatty acid content also increased. After extirpation of the spleen, the cholesterin content decreased and the fatty acid content increased to a less degree. In splenectomized animals the changes in the blood cholesterin were found to be similar to those following removal of the omentum.

**TUMORS OF OMENTUM.**—H. Rasmussen (*Acta chir. Scandinav.* 77: 61, 1935). The author reports 1 case of blood cyst, 4 cases of sarcoma, 2 cases of fibroma, 1 case of lipoma, and 1 case of tumor of the omentum in which the histological diagnosis was not clear. The symptoms vary, as they are due to compression of other organs. The diagnosis can be made if the possibility of such tumors was borne in mind and an x-ray examination is made of the colon and the urinary tract. The prognosis is good. The treatment is surgical.

**Liposarcoma with Metastases.**—C. Daniel and A. Babes (*Gynécologie* 34:5 (Jan.) 1935) were able to find only 1 case reported by Nienhuis, in 1925, and 1 case of malignant liposarcoma with metastases reported by Lubasch, in 1925. The writer describes a case in which the symptoms and signs were ascites, marked weakness, and chronic constipation. Examination showed a pelvic tumor. At operation, a tumor of the great omentum was found, which had formed metastases in the ovaries, Fallopian tubes, and broad ligaments. Histologically the cells were definitely of adipose tissue origin. They were of 2 types: (1) immature lipoblastic adipose tissue cells, and (2) cells grouped in vesicles which showed a marked polymorphism and contained fat. Among the latter were many large cells with multiple nuclei.

**PANCREAS.—ACUTE PANCREATITIS.**—According to E. H. Risley (*Maine M. J.* 26:110 (July) 1935) acute pancreatitis is not an uncommon disease. Its incidence is estimated to be around 1 per cent. of acute abdominal emergencies. Obstruction to and backing up of bile and pancreatic ferments into the pancreatic ducts are the probable etiologic factors producing the condition. The onset is usually sudden, occurring at the height of diges-

tion in subjects previously well. Pain out of all proportion to the physical signs is the predominating symptom. Shock is generally always present and is marked. Prolonged nausea and vomiting, with absence of marked abdominal signs at the onset, are also common. In addition to these symptoms, the author finds acute upper abdominal tenderness, with distention confined to the upper quadrants. Slate blue discolorations of the abdomen and thighs, a rise in pulse, temperature and leukocyte count, glycosuria and a high blood sugar, together with high amylase values, present the unquestionable picture of fulminating pancreatitis. Operation should never be done in the presence of the initial shock and if delayed from 4 to 8 days seems to give the best results. Mortality is high, varying between 50 and 90 per cent. Complications are frequent and convalescence is protracted.

Acute pancreatitis *in childhood* is discussed by R. H. Dobbs (Lancet 2:989 (Nov. 2) 1935). The author cites a case of acute pancreatitis in a child aged 12, contracted while under observation in the hospital, 2 weeks after a large collection of pus had been removed from a brain abscess. The *etiology* is discussed in the light of 14 reported cases, summaries of which are given. Acute pancreatitis in childhood is usually an accidental observation at an abdominal operation or postmortem. This is due partly to the rarity of the condition and partly to the fact that its causes are quite different from the commonest causes of acute pancreatitis in the adult. The *symptoms* and signs may be sufficiently distinct, however, to arouse suspicion of the true nature of the condition and can be confirmed by the urinary diastase test. Acute pancreatitis in childhood is but seldom etiologically related to a diseased biliary tract. Trauma accounts for many cases and *Ascaris lum-*

*bricoides* for a few, but in the majority no cause is found. Septic emboli lodging in the pancreas may occasionally be responsible. **Operation** should be undertaken promptly, allowing the rapid removal of destructive ferments and the blood-stained fluid which is always present.

**Surgical Pathology.**—F. Bernhard (Zentralbl. f. Chir. 62:71 (Jan. 12) 1935) points out that disease of the pancreas is believed to be preceded by disease of the biliary tract in almost 90 per cent. of cases. Entrance of bile into the main duct of the pancreas leads to activation of the pancreatic juice, with its serious effects, in only 20 per cent. of cases. Such penetration without detrimental effect has been found also during the course of other examinations, such as cholangiography. On the whole, the severity of the disease depends, not upon activation of the pancreatic juice in the excretory ducts, but on the activation of the juice in the gland lobules. The pancreas is irritated in disease of the biliary tract much more frequently than was formerly supposed. The irritation leads to the escape of ferments, which is evidenced by the appearance of diastase in the urine. This may be observed in every severe gall-stone attack. A persistent increase of diastase in the urine, therefore, is an absolute indication for operation in the early stages of the disease. The irritation extending to the pancreas from the biliary tract is considered to cause a vascular spasm which, in turn, leads to malnutrition of the gland tissue and the appearance of abnormal protein substances which activate the trypsin. The condition is aggravated by the vagus irritation which always accompanies an acute gall-stone attack and leads to increased secretion of pancreatic juice, with its deleterious effects upon the damaged organ. It is evident that if

the origin of pancreatic necrosis is believed to be exogenous, from the pancreatic duct, immediate operation is indicated, whereas if it is believed to be endogenous, from vascular spasm, delay of operation is indicated.

The pathologico-anatomical stages are: (1) pancreatic edema, (2) pancreatic edema with fat necrosis, (3) hemorrhage into the organ, (4) necrosis with areas of softening, and (5) discharge of tissue particles and suppuration. Three clinical stages are recognized: (1) the stage of pain, with characteristic radiation to the left shoulder; (2) the stage of ileus; and (3) the stage of peritonitis. Disturbances of external and internal secretions and disturbances of a general nature are of diagnostic significance. As the pancreatic juice reaches the blood, diastase is demonstrable and is found especially in the urine. The demonstration of trypsin in the blood and urine cannot yet be evaluated, but the test for lipase in the blood is recommended for larger clinics, because it is positive for a longer time than the test for diastase in the urine. Destruction of the islands of Langerhans and destruction of insulin by the trypsin are manifested by hyperglycemia and the excretion of sugar in the urine. The most exact findings are obtained by examination of the blood, especially glucose-tolerance tests. General disturbances are evidenced particularly by a marked increase in the leukocyte count, which may increase to from 50,000 to 60,000. An increase in the leukocyte count up to only 25,000 suggests a milder involvement which may subside spontaneously. Higher counts indicate severe disease. A reduction in the leukocytes indicates improvement. Only in the most severe cases does the organism become unable to produce a leukocytic reaction. The marked protein destruction occurring in severe cases is evi-

denced by the appearance of albumin and a large amount of brick-dust sediment in the urine. The appearance of urobilinogen and, at times, of urobilin, indicates the degree of liver damage which is, of course, of great importance in the *prognosis*. If oliguria or urinary suppression occurs with a corresponding increase in the residual nitrogen and indican in the blood, the operative prognosis is very poor.

With regard to the *indications for operation* there are still 2 opposing views. According to one, early operation is necessary. According to the other, the management should be expectant and operation performed when required in the given case. The two views may be bridged by modern diagnostic information since, on the basis of this information, mild cases may be recognized as such and treated conservatively. In the stage of pain and the stage of ileus in not-far advanced cases, it is always possible to achieve a recession of the pancreatic manifestations by conservative measures. In the peritonitis stage, operation should always be done. If an expectant course is decided upon, maximal doses of **morphine** should be given with maximal doses of **antropine** to overcome the vagus irritation and the vascular spasms. Even if this treatment is successful, **operation** should be performed later—in the period from the second to tenth week—for treatment of the existing disease and prevention of recurrence of the complications.

**Treatment.**—The treatment should consist of **early operation** to drain the pancreas and exteriorize the products of autodigestion. P. Brocq (*Presse méd.* 43:217 (Feb. 9) 1935) states that, in addition, any condition that can be recognized as a possible cause, such as disease of the gall-bladder and bile ducts, peptic ulcer, or duodenal stenosis, should be treated if the condition of the

patient permits further operative measures. In disease of the bile passages, **cholecystostomy** or **drainage of the common bile duct** is indicated. Since activation of the pancreatic juice is normally brought about by secretin, and this, in turn, appears in the duodenum in the presence of acid chyme from the stomach, the **stomach** should be **lavaged** with mild alkaline solutions to remove its contents and neutralize the acid. **General anesthesia** and **atropine** may be found of aid in reducing the amount of secretin. Some experimental evidence proves that certain salts and other medicaments may arrest the action of activated trypsin, but their use is still in the experimental stage. The *hypochloremia* should be treated by replacement with **chlorides**. *Hyperglycemia*, if present, should be treated by giving **insulin**.

The *results of surgical treatment* are discussed by F. F. Henderson and E. S. A. King (Arch. Surg. 30:1049 (June) 1935), who reviewed 60 cases of acute pancreatitis treated surgically at the Boston City Hospital during the past 15 years. They state that, in spite of much study, the results of treatment of this condition have not shown improvement to any degree comparable to that obtained in many other abdominal diseases. According to the literature, the mortality ranges between 40 and 80 per cent. In the cases reviewed, it was 53.3 per cent. It was the lowest in those in which operation was performed between the second and sixth days.

It appears from this series, which though small, is one of the largest to be reported, that acute pancreatitis is not as much of a surgical emergency as has been previously thought. The authors plan to be conservative in their treatment in the future and to delay operation to between the second and sixth days, choosing the time when the patient

appears to have reached maximum recovery from the initial toxemia.

In the cases reviewed, **cholecystostomy plus drainage of the pancreas through the gastrohepatic or gastrocolic omentum** proved to be the safest operation, and the use of **nitrous oxide oxygen** and **ether anesthesia** was followed by the lowest mortality.

**CHRONIC PANCREATITIS.**—G. de Tarnowsky and P. J. Sarma (Ann. Surg. 101:1342 (June) 1935) have analyzed 30 cases of chronic pancreatitis, illustrating the extreme difficulty of making a positive preoperative *diagnosis*. They state that in the case of a gland having such varied and all-important functions as the pancreas, it would be justifiable to assume *a priori* that the clinical manifestations of apathological condition would be many and almost pathognomonic. Unfortunately, however, the only 2 striking clinical manifestations of chronic pancreatitis are fat necrosis and pancreatic hemorrhage, both of which are present only in the most severe cases and demonstrable only at operation. With the exception of acute hemorrhagic pancreatitis and carcinoma of the head of the pancreas, surgical intervention in cases of subacute or chronic pancreatitis has not claimed the attention which these dysfunctions demand. *Symptoms*, when present, are often due to compression of organs.

Clinically, pancreatic dysfunctions can be divided into the following 3 main groups: (1) disturbances of external secretion interfering with the digestive apparatus in the subacute or chronic types or producing autolysis in fulminating cases of pancreatic apoplexy; (2) disturbances of internal secretion leading to glycosuria; and (3) carcinoma of the head of the pancreas.

**Etiology.**—That chronic pancreatitis must be the result of repeated attacks of acute subsiding pancreatitis is evident.

Retrograde infection of the pancreas through the lymphatics from the gall-bladder, appendix, or a duodenal ulcer is now regarded as extremely improbable. Pancreatic calculi gradually blocking one or both excretory ducts are so rare as to be surgical curiosities; only about 100 cases have been recorded to date. Hematogenous infection, though possibly explaining some of the fulminating cases of acute hemorrhagic pancreatitis, can be rejected insofar as chronic pancreatitis is concerned.

Direct continuity is an occasional etiological factor. The authors have found and freed adhesions associated with marked dilatation of the duodenum which they believed contributed to the syndrome of chronic pancreatitis. They believe that repeated, subsiding attacks of pancreatitis are due, in the vast majority of cases, to the entrance of bile into the pancreatic duct or ducts, and that as long as normal bile from the gall-bladder is discharged through the common duct into the duodenum, pancreatitis will not result. The work of Opie, Flexner, Archibald, Nordman, Cameron, and Noble has shown that: (1) bile plus gall-bladder mucin does not inflame the pancreas; (2) pure liver bile (blocked cystic duct) causes pancreatitis; and (3) infected bile (cholecystitis) causes pancreatitis.

The authors are of the opinion that chronic pancreatitis is the result of cholelithiasis with blockage of the cystic duct or of cholecystitis of sufficient severity to interfere with mucin formation or to destroy the gall-bladder mucosa. Blockage of the ampulla of Vater will produce the same result if cholecystitis is present. Arteriosclerosis, cysts or tumors of the pancreas, alcoholism, tuberculosis, syphilis, hemochromatosis, and hepatic cirrhosis seem to be possible etiological factors.

**Treatment.**—**Cholecystostomy** with **prolonged drainage** is the operation of choice in chronic pancreatitis. Without wishing to enter into the age-long controversy between the champions of routine cholecystectomies and the more conservative, perhaps more physiologically-minded, advocates of selective cholecystectomies, the authors state that a gall-bladder capable of functioning should never be removed if the head of the pancreas is enlarged, hardened, or edematous.

For prolonged drainage a rubber drain is left in the gall-bladder or cystic duct for from 10 to 14 days and the fistula is kept open from 4 to 6 weeks longer. In very chronic cases it may be necessary to continue the drainage for months.

**HYPERINSULINISM.**—According to A. O. Whipple and J. K. Frantz (Ann. Surg. 101:1299 (June) 1935), the first case of tumor of the island cells was reported by Nicholls in 1902. In 1922, Banting discovered insulin, and in standardizing the dosage of this substance he observed the symptoms of hyperinsulinism. In 1923, Harris suggested spontaneous hyperinsulinism as a clinical possibility, and in 1927, Wilder attributed hyperinsulinism to a pancreatic tumor. In later investigations an insulin-like substance was found in pancreatic tumors.

In the literature the authors found 75 cases of hyperinsulinism. In 62 the condition was associated with a tumor. Most of the tumors were small (1.5 cm. in diameter), but one of them weighed 500 grams. The neoplasms are reddish and usually found in the tail of the pancreas, close under the capsule of the gland. They are usually grossly encapsulated, but some of them are without a definite capsule. As in 3 of the cases reported in the literature, metastases were found; the tumors apparently in-

clude frank pancreatic carcinomas as well as benign adenomas.

The authors report on 8 tumors removed from 6 patients with hyperinsulinism. They classified these growths as adenomas. In 3 of the neoplasms an infiltrating tendency was noted. Functional activity of the tumor cells was proved by the fact that the patients no longer suffered from hyperinsulinism after removal of the tumors. However, the authors were unable to extract an insulin-like substance from the growths.

**Symptomatology.**—A report of 5 cases of *adenoma of the islands of Langerhans* is made by L. Feinier, S. E. Soltz and P. Haun (Bull. Neurol. Inst. New York 4:310 (Oct.) 1935). In all the diagnoses was confirmed by operation. Four of the patients were women. The ages at the time of onset of the condition ranged from 22 to 47 years, and the duration of disease up to the time of operation from 6 months to 12 years.

The clinical picture of adenoma of the islands of Langerhans is a definitely recognizable neuropsychiatric syndrome consisting of : (1) disturbance of consciousness, (2) psychic symptoms, (3) superfluous movements, (4) objective neurological clinical signs, and (5) markedly low blood-sugar values and dextrose-tolerance curves of a plateau type.

The clinical features are attacks of confusion and exhaustion, superfluous movements, and considerable organic mental reaction with fear, irritability, restlessness, variations in the threshold of awareness, changes in behavior, and some degree of amnesia for the entire episode. The mental manifestations are of the toxic type, paroxysmal and transitory, and associated with other definite symptoms, including profuse diaphoresis, weakness, dizziness and occasional transitory aphasia or paraphasia,

diplopia, and headache. Between attacks, evidences of mental deterioration may sometimes be noted. The superfluous movements vary from convulsive to tic-like, semipurposeful, and aimless or bizarre manifestations, accompanied by clouding of consciousness, varying from dreamy states to attacks of unconsciousness.

In the 5 reported cases the objective neurological signs were as follows: diplopia in 3, nystagmus in 3, slight obscuration or blurring of the optic papillæ in 4, inequality of the deep reflexes in 3, Babinski and Chaddock signs in 2, convulsions or other definitely superfluous movements in 4, and transitory aphasia in 3 cases. Clouding of consciousness occurred in 5 of the cases, and in 3 it amounted to attacks of unconsciousness.

The symptoms present paroxysmal exacerbations which are characteristically relieved by the intravenous administration of dextrose. In all of the authors' cases the level of the fasting blood sugar showed a marked reduction and dextrose-tolerance tests revealed a curve of the plateau type with a delayed fall. It is to be emphasized that the fasting blood-sugar value is not always markedly low. Certain variations may be anticipated and are consistent with the diagnosis of adenoma of the pancreas. A slight to moderate degree of temporary relief following **special diets and extra feedings** may be noted and, more specifically, a marked temporary improvement following intravenous injections of **dextrose**. Despite such palliative therapeutic measures, the course of the disease continues to be progressive and presents recurrent typical paroxysmal manifestations.

The typical clinical signs are dependent on pathological involvement of the brain. A hypoglycemic state resulting from hyperinsulinism appears obvious, but the exact mechanism responsible for

the alteration in brain function and structure remains to be established. In the absence of a gross defect of the liver, no other endocrine disease, with the possible exception of severe involvement of the adrenal glands, is likely to cause difficulty in the differential diagnosis.

Because of the almost exclusively neuropsychiatric manifestations, patients presenting the symptoms characteristic of pancreatic adenoma are very likely to be admitted to neurological and psychiatric hospitals and clinics.

In all of the 5 cases reported by the authors, removal of the tumor was followed by recovery. In 4 cases a single tumor was found. The neoplasms were well encapsulated, very vascular, and from 1 to almost 2 cm. in diameter. Their locations varied and bore no relationship to the symptoms. The variation in position, small size, and occasional multiplicity of such neoplasms show the necessity for careful examination by both inspection and palpation of the entire pancreas at the time of operation.

**Diagnosis.**—J. A. Berry (Brit. J. Surg. 23: 51 (July) 1935) divides cases of hypoglycemia into: (1) those due to functional hyperinsulinism resulting from an increase in the number, size, or activity of the islands of Langerhans; (2) those due to the presence of an adenoma or carcinoma of the pancreas; and (3) those due to pituitary, adrenal, hepatic, or other factors.

Except in cases in which an adenoma is removed, the surgical treatment of spontaneous hypoglycemia is disappointing. In cases of hyperinsulinism which have not responded to surgical treatment it is necessary to consider the possibility that a small adenoma is buried in the head of the pancreas where, on account of its size, it would be difficult or impossible to find.

In most of the cases reported in the literature there was no improvement

following operation because the amount of pancreatic tissue removed was too small. In Wornack's case, in which about one-half of the gland was removed, and in the case reported by Graham and Hartmann, in which from 80 to 90 per cent. was removed, improvement resulted. It is probable that, for satisfactory results, half of the pancreas should be removed. The removal of considerably more than half of the pancreas might render the patient permanently diabetic. In the author's case the diabetic tendency lasted for only a short time. After its disappearance there was apparently an increased activity of the remaining insulin tissues and the patient's condition seemed to have returned to its former state. Since then the blood-sugar curve has become almost normal.

The following hypotheses are advanced:

1. In a moderately severe case of functional hyperinsulinism, adequate resection, probably of more than half of the pancreas, is necessary to alleviate the symptoms.

2. In the diagnosis of functional hyperinsulinism, increasing doses of glucose are necessary in preparing the blood-sugar curves, and the curves are lower with the large doses.

3. In functional hyperinsulinism, starvation causes a rise in the blood sugar.

It is suggested that these two tests may be of value in distinguishing functional hyperinsulinism from adenoma and carcinoma of the pancreas.

**Treatment.**—A simplified technic for subtotal pancreatectomy is given by J. M. McCaughan (Ann. Surg. 101: 1336 (June) 1935) as follows:

Shortly before operation the patient is given 500 c.c. (1 pint) of a 10 per cent. solution of dextrose intravenously, and the stomach is thoroughly emptied of fluid and gas by aspiration. The preliminary medication consists of  $\frac{1}{4}$  grain (0.01 Gm.) of morphine sulphate



and  $\frac{1}{150}$  grain (0.4 mg.) of **atropine sulphate** given hypodermically. **Ether anesthesia** is used by preference because of its effect in sustaining and even elevating the normal level of the blood sugar. A long left midrectus incision is made. The gastrocolic omentum is divided transversely and a gauze pack is placed against the stomach, which is rotated slightly and drawn upward by an assistant. A second pack is placed over the transverse colon, which is then displaced downward. The small of the back is elevated by means of the operating table backrest. The resection is begun by dividing the peritoneal investment along the lower margin of the pancreas and grasping the tail with a suitable forceps and drawing it slightly forward and downward. Temporary tape ligatures are passed about the splenic vein and splenic artery. The subsequent dissection is directed toward the freeing of the tail and the body of the pancreas from the splenic artery and vein, because it not only enables one by traction and countertraction to display the numerous tributary vessels supplying the tail and body of the pancreas by placing them on a stretch, but it also gives immediate control of the vascular pedicle of the spleen should either vein or artery be inadvertently wounded. The tributary vessels may be divided between ligatures, either an aneurism needle or an artery forceps being used to introduce the suture underneath the vessel. The large pancreatic artery should be secured early in the dissection. The dissection is continued until the region of the junction of the body with the head is reached. As much of the gland is removed as seems indicated by the severity of the case at hand. An assistant holds the body of the pancreas in the grasp of a rubber-covered right angle forceps, just tightly enough to control bleeding. The pancreas may then be divided with a V-type incision and the stump closed with either an interrupted mattress suture or running lock stitch, giving satisfactory hemostasis. A rubber tissue drain is introduced to the bed of the resected portion and the gastrocolic omentum is closed loosely about the drain. After operation, the blood sugar should be maintained at normal levels by the administration of **carbohydrates**.

A. O. Whipple and J. K. Frantz (*Ibid.* 101:1299 (June) 1935) operate under **spinal anesthesia**. They make a transverse incision through both recti and divide the gastrocolic omentum widely.

They then make a careful search for adenomas, especially in the tail and body of the pancreas. If one such tumor is found, they search for others. If no adenomas are found, they remove about two-thirds of the pancreas with the Percy cautery. **Splenectomy** and **ligation of the splenic artery** greatly reduce *hemorrhage* from small vessels. **Drainage** is advisable in partial pancreatectomy, but is not necessary in the removal of an adenoma.

### CARCINOMA OF PANCREAS.

—*Diagnosis*.—C. A. Sones (J. Iowa. M. Soc. 26:82 (Feb.) 1936) points out that there is no clinical syndrome singularly characteristic of carcinoma of the pancreas. There are no physical, laboratory or x-ray signs which in themselves are final in the diagnosis. In a case of cachexia with loss of weight and strength, deep progressive jaundice, hard boring epigastric pain radiating to the back and affected by posture, palpable epigastric tumor which is fairly well fixed and tender, palpable gall-bladder, abnormal blood sugar level and positive x-ray observations, all the cardinal symptoms and signs are present for a reasonably accurate clinical diagnosis of carcinoma of the pancreas; but the actuarial computation by percentages would reveal the fact that all these features are present in the same case in only 1 out of at least 200 cases. In the great majority of cases many of these are lacking or indefinite, so that a satisfactory diagnosis is difficult or impossible; but it seems fair to say that with cachexia, weight and strength loss as one, in addition to any two of the remaining features, there is sufficient evidence for a presumptive diagnosis.

*Treatment*.—A. O. Whipple, W. B. Parsons and C. R. Mullins (Ann. Surg. 102:763 (Oct.) 1935) review certain factors which have compromised the success of **radical removal** of car-

cinoma of the ampulla of Vater and the head of the pancreas. The first of these was the mistaken belief that the flow of pancreatic juice is essential to life, which led surgeons to reestablish this flow into the duodenum or jejunum by implanting the resected head of the pancreas or the cut end of the duct into the upper intestine. In the human subject the activation of pancreatic ferments by duodenal contents compromised any type of anastomosis, especially around the posterior aspect of the duodenum devoid of peritoneum. A second factor was the attempt to carry out the excision of these tumors in one stage, whatever the method used. The victims of these tumors are, as a rule, deeply jaundiced, depleted, undernourished, and asthenic, and are suffering from a hemorrhagic diathesis and severe liver damage. The majority of these cases cannot survive such a major operation until the associated symptoms have been relieved. In recent years this factor has been recognized and a preliminary short-circuiting operation to relieve jaundice has been carried out.

The authors report 3 cases of carcinoma of the ampulla of Vater. The first 2 patients died as a result of a failure of the operative procedure employed. The third patient, who was subjected to an improved technic, was reported well more than 6 months after the last operation. The technic employed by the author is as follows:

Under **spinal anesthesia** induced with **pantocaine** a right rectus or an epigastric midline incision is made. A posterior gastroenterostomy is then performed and followed by ligation and section of the common duct below the cystic duct after the patency of the cystic duct has been determined. A long black ligature is left as an indicator on the lower stump of the sectioned common duct. **Cholecystogastrostomy** is done to the anterior surface of the stomach well away from the pylorus, the anastomotic opening being made at least 2 cm. in diameter in order to prevent

subsequent stenosis and cholangitis. Three or four weeks later a second operation is carried out under spinal anesthesia and through a transverse incision made above the umbilicus, through both recti if necessary. Ligation of the pancreaticoduodenal and gastroduodenal arteries is followed by resection of the descending portion of the duodenum with inversion of the upper and lower ends and a V-shaped excision of the pancreas wide of the growth, together with the common duct, and use of the silk ligatures as a guide to the lower cut end of the duct. The cut end of the duct of Wirsung and the duct of Santorini, if present, are ligated and the two cut surfaces sutured with interrupted sutures of fine silk. The bed of the resected duodenum is drained with a cigarette drain. Throughout these steps a silk technic was employed, the finest silk being used for all but the large arteries.

E. S. Judd and M. T. Hoerner (Arch. Surg. 31:937 (Dec.) 1935) have performed a palliative operation in 14 of 21 cases of carcinoma of the ampulla of Vater at the Mayo Clinic. **Cholecystogastrostomy** was performed 12 times and **cholecystoduodenostomy** and **choledochoduodenostomy** once each. Four of the patients did not recover from the operation, but the average postoperative life of those who did was 13.9 months. In the 7 remaining cases in this group the lesion appeared to be amenable to complete extirpation. Consequently, resection of the ampulla of Vater together with the tumor was carried out. Four of the 5 patients who survived the operation were completely relieved of their symptoms, and lived for 1 year and 3 months, 2 years and 2 months, 2 years and 2 months and 3 years, respectively. One patient was not traced. For the sake of comparison, the authors selected 158 cases of carcinoma of the head of the pancreas, a condition closely related to malignant lesions of the ampulla of Vater. Some form of anastomosis between the biliary tract and the intestine was performed in these cases. In 64 cases the differentiation of carcinoma and chronic

pancreatitis could not be made with certainty, although in the opinion of the surgeon a malignant condition was the more likely in the majority of cases. The mortality at the hospital for this series of palliative operations was high. The patients who survived the operation, however, were relieved of their most troublesome symptoms, pain, jaundice, pruritus and episodes of chills and fever, except in a very few instances. Only 4 per cent. of the surviving patients derived no benefit from the operation. These patients were the ones in whom the carcinoma was farthest advanced at the time of operation, and most of them died within 3 months after the procedure. The average length of life after leaving the hospital for the patients with verified carcinoma of the head of the pancreas was 10.2 months. The patients in whom carcinoma of the head of the pancreas and chronic pancreatitis could not definitely be distinguished, lived, on an average, 11.9 months. The discrepancy between these figures could be accounted for by the inclusion in the latter group of several patients with simple pancreatitis. That some patients with a questionable diagnosis did survive from 3 to 6½ years lends weight to this opinion. Nevertheless, the number of incorrect diagnoses in a large series of cases is relatively few, for the surgeon can form a rather accurate opinion of the condition with which he is dealing but is refrained from offering a dogmatic statement because a specimen for biopsy was not taken.

**ABERRANT PANCREATIC TISSUE.**—The discovery of aberrant pancreatic tissue at operation or autopsy has been reported periodically since such tissue was first described by Klob in 1859. The literature to date contains records of approximately 200 cases. C. D. Branch and R. E. Gross (Arch.

cases in which the aberrant tissue was found in various locations in the wall of the gastrointestinal tract.

In the majority of cases reported previously, the aberrant tissue was in the upper portion of the gastrointestinal tract, and in almost 80 per cent. of these it was in the wall of the stomach, duodenum, or jejunum. In the majority of the remaining cases it was in the ileum, appearing particularly in diverticula. In a few cases it was found in the omentum, the mesenteric fat, an umbilical fistula, the wall of the gall-bladder, or the splenic capsule. Thus, it is seen that in most instances it occurred in a part derived from the foregut.

Various theories as to the *origin* of the aberrant pancreatic tissue have been advanced. The authors believe that such tissue is a congenital abnormality which arises either as an anomalous enlage or as an inclusion of primitive pancreatic tissue in a portion of the foregut or its derivatives, and does not represent a stage of normal fetal growth.

Of the authors' 24 cases, 12 were those of males. The ages of the patients ranged from 8 days to 82 years. In 5 cases the abnormality was discovered at operation and in 19 at autopsy. In 2 cases it was located in the gastric wall. In both of these, partial resection of the stomach was done under the impression that the nodular mass was carcinomatous. In 1 case the pancreatic tissue was found in the pyloric ring. In 10 cases it occurred in the duodenum, and in 1 of these it was in a duodenal diverticulum. In 4 cases it occurred in the jejunum, and in 1 case in the wall of the ileum. In the remaining 6 cases it occurred in a Meckel diverticulum.

Microscopic examination showed the tissue to contain ductal and acinar elements with a structure closely resembling that of normal pancreatic tis-

Langerhans were present, but in the remaining 15 none was seen.

Aberrant pancreatic tissue may occasionally cause *symptoms*. In a purely mechanical manner it may produce pyloric or intestinal obstruction. Cases of intussusception in which the pancreatic tissue acted as the leading point have been reported. Some believe that certain intestinal diverticula are formed because of weakening of the musculature of the intestinal wall by the aberrant pancreatic tissue. Inflammatory reactions arising in aberrant pancreatic tissue may cause symptoms simulating those of peptic ulcer or appendicitis, depending on the site of the tissue. Cases of malignant degeneration of abnormally situated pancreatic tissue have been reported.

Of the authors' 24 cases, 4 had important pathological significance. In 1 of the latter the nodule caused pyloric obstruction, and in 3 it was the site of ulceration in the stomach or duodenum. The 24 cases are reported briefly.

**PERITONEUM.—PERITONITIS.—*Prophylaxis*.**—From the experimental and clinical evidence on which H. L. Johnson, G. K. Coonse, J. B. Hazard, P. S. Foisee and O. Aufranc (Surg. Gynec. and Obst. 62: 171 (Feb. 1) 1936) base their paper, they state that they have definitely proved that **amniotic fluid concentrate** most effectively meets the requirements to establish peritoneal immunity against infection and adhesions. The **bacterial vaccine** of Rankin and Bagen is best used preoperatively from 48 to 72 hours before celiotomy, and the protection afforded by its introduction is attained at the cost of a considerable physiologic and clinical upset and a long immunizing interval. The brief immunization interval required in the use of amniotic fluid concentrate makes it adaptable

for operative as well as preoperative introduction.

***Treatment of General Peritonitis.***—T. R. Sealy (Texas State J. Med. 31: 284 (Aug.) 1935) considers the most effective treatment of acute general peritonitis, after **removal of the source of infection** and providing ample **drainage**, is to get the patient's intestine to function. Toxemia is the chief cause of death and is due not to the original source of infection, but to absorption of toxic substances from the intestine above an obstruction and from the inflamed peritoneum. Other causes of death are dehydration, starvation, and lethal deficiency of sodium and chlorides in the body.

The problem of draining the abdominal cavity in cases of general peritonitis is still unsettled. When the exudate becomes very purulent and contains intestinal matter, necrotic tissue or some other foreign material, it should be removed at the time of operation. One of the strongest arguments against drainage of the abdominal cavity for the removal of exudate not removed at the time of operation is based on the fact that all drains are completely walled off from the rest of the abdomen within 10 to 12 hours. Drainage can be accomplished best by inserting a drain between the anterior abdominal wall and the omentum, where it will not lie in contact with the intestines.

O. Kapel (Zentralbl. f. Chir. 62: 2053 (Aug. 31) 1935) employed **serotherapy** in all cases of diffuse, free perforation peritonitis, in the majority of cases of localized perforation peritonitis, in cases in which there was an accumulation of pus around the vermiform process and, finally, in cases in which large portions of the appendix were gangrenous so that the bacteria could penetrate. There was no change in the mortality rate. In the patient who recovered, the signs of

general intoxication were less severe and recovery was more rapid. Kapel is inclined to believe that these serums are only antibacterial, not antitoxic.

**PRIMARY PERITONITIS IN CHILDREN.**—J. S. Leopold and F. Castrovinci (J. Pediat. 7:187 (Aug.) 1935) report 11 cases of primary peritonitis (7 pneumococcic and 4 streptococcic) that occurred in female children between the ages of 2 and 10 years. The clinical pathologic picture strongly suggests that the organisms enter the abdominal cavity at the ileocecal-appendical region.

**Diagnosis.**—Abdominal puncture should be performed oftener and early to establish a diagnosis. They believe the objections to puncture are theoretical.

**Treatment.**—**Operation** was performed in 9 cases with a mortality of 75 per cent. One case of streptococcic peritonitis recovered without operation.

**ACUTE PERITONITIS.**—J. J. Chydenius (Acta Soc. med. fenn. duodecim (Ser. B, fasc. 1-3, art. 5) 23:1, 1935) reviewed 100 cases of acute free peritonitis of different types. The majority were cases of diffuse peritonitis due to abortion. From 1919 to 1924, conservative treatment was used and all but 1 of the 24 patients died. From 1925 to 1935, 70 cases of *abortion peritonitis* were treated. In 18 hopeless cases, operation was not performed, and in 12, which were very unfavorable, only **drainage** was done. In 40 cases, **radical operation with vaginal drainage** was performed, and, in early cases, with high peritonization. Fifteen of the 40 patients recovered. Diffuse streptococcic peritonitis was present in at least 10 of the cases terminating in recovery. Operations performed in the first 4 months of pregnancy terminated favorably. In cases of abortion and premature delivery at a later date, the *prognosis* was very unfavorable. The time that elapsed between

the abortion and the beginning of the peritonitis was a very important factor. In almost all of the fatal cases, the peritonitis developed during the first week after the abortion; in cases with recovery it developed later. The prognosis improves rapidly with the increase in length of time between abortion and the peritonitis. Pelvic thrombophlebitis discovered nearly always in the later months of pregnancy makes the prognosis unfavorable. The best results are obtained in cases in which expectant treatment is employed until a free peritonitis becomes an encapsulated pelvipерitonitis.

**GENERALIZED PERITONITIS.**—Five cases of generalized peritonitis due to rupture of pyosalpinx are reported by A. Soimaru (Gynécologie 34:21 (Jan.) 1935).

**ETIOLOGY.**—It occurs in women between 20 and 35 years of age. The rupture may be a traumatic rupture of a chronic pyosalpinx or the perforation of a pyosalpinx following an acute inflammation with ulcerative lesions in the tubal wall. The latter is more dangerous and virulent. About 3 per cent. of tubal infections rupture.

**DIAGNOSIS.**—There is usually a definite history of tubal infection, otherwise the condition is often believed to be due to appendicitis. In many cases the rupture of the pyosalpinx is preceded by an increase in the pelvic pain and a rise in temperature. At the time of rupture the pain becomes more severe and the swelling disappears. The patient may collapse. There is generalized muscular rigidity.

**TREATMENT.**—The pyosalpinx is usually bound down by adhesions in chronic cases, thus limiting the spread of the infection. When the tubal infection shows evidence of the development of a pyosalpinx, with the danger of rupture, Soimaru prefers **operation**. If rupture occurs, operation should be per-

formed immediately. **Removal of the tube and ovary** on one or both sides, with **drainage**, is the operation of choice.

**PERITONITIS OF PYELO-RENAL ORIGIN.**—R. Couvelaire (J. de chir. 47:392 (Mar.) 1936) reviews 49 cases and reports 3, calling attention to the fact that in diffuse peritonitis it is important to remember that retroperitoneal organs (kidney, renal pelvis, ureter) may be the primary focus as well as intraperitoneal viscera.

**TREATMENT.**—Recovery resulted only when both the peritoneum and the abscess around the kidney were **drained**. The results were best when **nephrectomy** was done in addition to drainage, the condition of the other kidney being known. **Nephrostomy** is therefore advisable.

**STREPTOCOCCIC PERITONITIS.**—In 8 cases of streptococcic peritonitis studied J. Felsen and A. G. Osofsky (Arch. Surg. 31:437 (Sept.) 1935) there was a definite history of sore throat. In 2 adults the organism was nonhemolytic, but the general features were the same with both the viridans (5 cases) and the nonhemolytic type (3 cases). The authors believe that it occurs through the focal hemorrhagic and ulcerative lesions in the intestine. The abdominal symptoms came on in about 6 days. The onset was abrupt with temperatures up to 107.8° F. (42.1° C.). The initial leukocyte count was high. The mortality was 100 per cent. The pathological picture was that of a streptococcic septicemia with profound toxic effects.

**PNEUMOCOCCIC PERITONITIS.**—I. Díaz Bobillo (Semana méd. 1:592 (Feb. 20) 1936) reports 7 cases *in infants* from 6 months to 2 years of age. It was primary in 2 cases, secondary to pneumonia, pleurisy and pericarditis in 3, and associated with pleuropulmonary

pneumococcic infection in 2 cases. C. K. Schaanning (Acta chir. Scandinav 77:256 (Nov. 15) 1935), reporting on 37 children, believes infection by uterine tubes occurs seldom. It seems likely that infectious material is swallowed and the peritoneum becomes infected by way of the intestine. Hematogenous infection of the intestine is possible. Lungs and tonsils are frequently the primary foci of infection. A lymphogenous infection occurred in several cases. In patients with otitis media, the hematogenous route of infection must be considered.

Three cases of *encysted pneumococcic peritonitis* with a subacute or chronic course are reported by A. Chauvenet, P. Broustet, and Cornette de Saint-Cyr (J. de méd. de Bordeaux 113:303 (Apr. 30) 1936). It is more common in older adults, having no relation to sex. As a rule, it follows an infection of the lungs or pleura. The symptoms are few in the beginning. The condition must be differentiated from chronic appendiceal abscess, tuberculous peritonitis, hydatid cyst, pyonephrosis and empyema of the gall-bladder.

**SUBPHRENIC ABSCESS.**—R. H. Overholt and J. C. Donchess (New England J. Med. 213:294 (Aug. 15) 1935) report on 25 cases of subphrenic abscess treated at the Lahey Clinic.

**Etiology.**—Subphrenic abscess results when infection already existing in the peritoneal cavity spreads into the subdiaphragmatic space. Infection in the pelvis or the right lower quadrant of the abdomen may spread upward laterally to the cecum and ascending colon. From the region of the gall-bladder or pylorus infection may spread to the right subhepatic area and extend over and under the liver to the posterosuperior or anterosuperior space. The important part played by pressure changes in the upper abdomen has not been emphasized. Overholt has shown that during quiet

respiration the intraperitoneal pressure in the upper abdomen is less than the atmospheric pressure. Therefore, pus that has reached the upper abdomen may be sucked up to the subphrenic space.

**Symptoms.**—These consist of discomfort in the upper part of the abdomen, dyspnea, hiccough, and referred pain in the chest, shoulders, or neck.

**Differential Diagnosis.**—Differentiation should be made from generalized peritonitis, liver abscess, perinephritic abscess, thoracic emphysema, postoperative massive collapse of the lungs, and unilateral atelectasis.

**Treatment.**—It is desirable to keep the patient in a half-sitting position. The authors advocate the operation of Ochsner.

**INTRAPERITONEAL BILIARY EFFUSIONS WITHOUT APPARENT PERFORATION OF BILIARY TRACT.**—When, in exploration of the peritoneal cavity, a generalized peritonitis with free bile in the peritoneal cavity is found, the stomach, duodenum, liver, and extrahepatic biliary tract should be immediately examined for perforation, according to I. Sabadini and E. Curtillet (*J. de chir.* 45:191 (Feb.) 1935). The authors report 4 cases.

**Etiology.**—The condition occurs more frequently in women than in men. As a rule, there is a history of intestinal disturbance over a period of years. Cholelithiasis is almost invariably present, and commonly there is an occlusion of the common bile duct either by a stone or a pancreatic lesion.

**Symptoms.**—The onset of the illness is very sudden and associated with excruciating pain, which is generalized over the epigastrium and not referred to any particular point. The abdomen is very tender and presents a generalized muscular defense. Bilirubin may be recovered from the urine.

**Treatment.**—All cases treated conservatively have proven fatal. In cases treated surgically the prognosis is rather good. The operative procedure is **drainage** of the abdominal cavity with **cholecystostomy** and **cholechochotomy** or **cholecystectomy** and **cholechochotomy**.

**PERITONEAL ADHESIONS.**—E. Kaufman (*Beitr. z. klin. Chir.* 161: 599, 1935) divides peritoneal adhesions into 2 groups, *i. e.*, the *spontaneous* and the *postoperative*. Spontaneous adhesions are of traumatic, congenital, and inflammatory origin. Traumatic adhesions, which form as the result of blunt traumas to the abdominal wall, are of particular importance from the standpoint of insurance. Spontaneous adhesions are usually of inflammatory origin.

**Treatment.**—Surgery is employed only for interference with gastrointestinal motility and then is limited as much as possible. Postoperative adhesions were found by the author in 88 per cent. of 509 reoperations. They occurred most often in the right upper and lower quadrants and very often involved the omentum. The symptoms of postoperative adhesions he divides into 3 groups: (1) general complaints due to adhesions, (2) disturbances of motility, and (3) intestinal obstruction. The treatment of the first group is **diathermy** first and **surgery** last. In the second group with sudden attacks of ileus due to intestinal kinks which, as a rule, relax spontaneously, **surgery** may be necessary. In the third group with intestinal obstruction, the time for operation is difficult to determine. At the beginning, the surgeon hesitates to operate, and later it is often too late. Of chief importance in the *prevention* of adhesions are the **operative technic**, **early stimulation of peristalsis**, and the **avoidance of iodine**.

**TUMORS AND CYSTS.**—*Pseudomyxoma of Peritoneum.*—T. Antoine (Ztschr. f. Geburtsh. u. Gynäk. 111:37 (June 20) 1935) describes 7 cases. Pseudomyxoma may originate in the appendix as well as in the ovary. The jelly-like secretion is produced by the epithelium. The penetration of the jelly-like substance into the connective tissue is caused by a rarefaction of the connective tissue with compensatory filling of the spaces with this substance.

**TREATMENT.**—The author states that the surgical treatment should be radical and followed by x-ray irradiation.

**Lymphatic Enteroperitoneal Cysts.**

—**PATHOGENESIS.**—A recent classification by Luly divided such cysts into: (1) those derived from the lymphatic system, *viz.*, lymphochylangiomas; (2) encysted hematomas; (3) parasitic cysts; (4) gaseous cysts; and (5) cysts of embryonic origin (ectodermal, mesodermal, endodermal, or mixed cysts, teratomas, and fetal inclusions). According to S. Ferrandu (Clin. chir. 12:105, 1936) the cysts originate in lymphatic channels in which there is a preëxisting ectasia, due to circumscribed malformations in the wall. Hemorrhage occurs in this region from the small blood vessels of the wall, and under the influence of pressure the congenital ectasia is transformed into a cystic cavity which at first contains hemorrhagic lymph and later a pseudochyle or serum. Occasionally, especially in the adult, these cysts may be related to hypertension, toxic-infective states, dystrophies, or degeneration of the blood-vessel walls, all of which conditions may lead to hemorrhage. In the peritoneum and intestines hemorrhage is favored by movements of the intestines.

**Retroperitoneal Hematomas.**—**ETIOLOGY.**—Trauma is an important factor, although spontaneous nontraumatic hematomas are found in the kidney

region even more often than the traumatic. In a reported case of unilateral adrenal hemorrhage the patient had cirrhosis of the liver and arteriosclerosis of the coronary artery.

**SYMPTOMS.**—C. C. Fleischer-Hansen (Hospitalstid. 78:973 (Sept. 17) 1935) reports a case of partially calcified perirenal hematoma in which the tumor, originating after trauma, endured for 25 years without special symptoms. Renal function and urine were normal and the pyelogram showed slight changes. Pain and swelling in some degree is always present. In the spontaneous nontraumatic hematomas the onset is sudden, with violent pain in the renal region. Possible infection of the hematoma will show signs and symptoms of infection.

**DIAGNOSIS.**—Perirenal hemorrhage should be suspected when there is pain and swelling in these areas following trauma. The *differential diagnosis* should be made from renal tumor, perirenal abscess or ileus.

**TREATMENT.**—Traumatic cases are treated conservatively unless the hematoma is very large, then extraperitoneal excision is called for. Infection of the hematoma calls for surgical treatment. Operation may be indicated later, often after years, because of cyst formation, pseudohydronephrosis, calcification, deficient resorption or other complications. The incision is made in the lumbar region, and drainage of the hematoma and possibly nephrectomy done. The reported mortality is about 60 per cent. Early diagnosis and treatment are important for a better prognosis.

**SPLEEN.—HEMOLYTIC HYPERSPLENIA (Acquired Hemolytic Icterus).**—L. Heilmeyer (Deutsches Archiv. f. klin. Med. 178: 89 (Oct. 6) 1935) reports this definite disease entity



in the *etiology* of which he calls attention to the significance of severe infections and endocrine disturbances. A case is cited of hemolytic anemia with splenic tumor which developed after a severe thyroid and hypophyseal disturbance. The *symptoms* of this disorder are severe hemolytic anemia, with considerable increase in the blood exchange (reticulocytosis of from 100 to 400 per 1000 and urobilin elimination in feces of from 700 to 3000 mg.); absence of hepatic changes; absence of bilirubinuria; reduction of osmotic resistance; microspherocytosis; splenic tumor; sudden onset of the disorder and lack of symptoms of congenital hemolytic icterus in the history; absence of constitutional hemolytic signs; absence of similar disturbances among the relatives; and cure after splenectomy.

**SPLENOMEGALY IN CHILDREN.**—R. M. Smith and S. Farber (J. Pediat. 7:585 (Nov.) 1935) observed 15 children with splenomegaly and early hematemesis. The primary pathologic lesion is considered to be portal or splenic vein obstruction due in most instances to thrombophlebitis secondary to infection in some other part of the body. Attention is called to the decrease in size of the spleen after hemorrhage and the return to the previous or greater size after restoration of the blood loss. There was no cirrhosis of the liver or ascites.

**Treatment.**—Splenectomy does not prevent recurrence of hemorrhage. Ligation of vessels going to the stomach and esophagus offers a further means of treatment with the possibility of greater success in the prevention of recurrent hemorrhage.

**SPLENECTOMY.—Effects of Removal of Normal Spleen.**—A study of 100 cases by E. Ask-Upmark (Svenska läk.-sällsk. handl. 61:197, 1935) showed no increase in susceptibility to infections

or to malignant tumors. A tendency to rapid exhaustion was not infrequently present. In 10 per cent. of the cases there were digestive disturbances, changes in body weight, disturbances in the nervous system and metabolic activities. Anatomically, physiologically, and clinically his investigations indicate that the spleen, while not necessary to life, should be removed only on vital indication.

**Results of Splenectomy.**—L. Wieden (Mitt. a. d. Grenzgeb. b. d. Med. u. Chir. 44:13, 1935) reports on 81 splenectomies employed for various conditions. In 21 cases of *injury* of the spleen, 8 died soon after the operation and 13 lived. Two patients with *perforating splenic abscesses* died of peritonitis after the operation. Seven patients with *infarction* of the spleen were operated upon without this diagnosis. Three died soon after the operation, 3 were discharged as cured, while 1 could not be traced. Of 5 patients with splenic infarction occurring as a sequela of endocarditis, 4 died after the operation and 1 could not be traced. Four patients with *thrombophlebitic enlargement* of the spleen and *thrombosis of the splenic vein* were cured. Three splenectomies were performed for *tuberculosis of the spleen*, the patients being discharged as cured. A patient with *sarcoma of the spleen* died after the second operation.

Of 9 patients subjected to splenectomy for *thrombopenia*, 4 are well, 2 recovered, but died later of unknown causes, 2 could not be traced, and 1 died soon after the operation. After splenectomy the number of thrombocytes at first increase markedly, but later drop to a level slightly lower than normal. In 1 case of splenopathic thrombopenia only occasional small hemorrhages occurred after removal of the spleen. Splenectomy was performed for *malignant thrombopenia*, *hemorrhagic aleukia*, the patient dying soon after the opera-

tion. In a case of *hemoglobinuria* there was no improvement after 9 weeks. In 13 cases of *hemolytic icterus*, 2 patients died after the operation and 11 were cured or greatly benefited. One died later of unknown cause. In 2 cases of *cirrhosis of the liver with splenomegaly*, 1 youth died soon after operation, the other patient dying 2 years later of unknown cause. In 9 cases of *pernicious anemia* the results were very satisfactory. One case of *aplastic anemia* died soon after operation. Of 2 cases with *myeloid leukemia*, 1 died 3½ years later and the other is living and able to work 6 years after the splenectomy.

IN CHILDHOOD. — G. C. Penberthy and T. B. Cooley (Ann. Surg. 102:645 (Oct.) 1935) performed splenectomy in 2 cases of *erythroblastic anemia*. The course of the anemia was not appreciably altered. There was an increase in circulating normoblasts. The patients were relieved from the weight of the enlarged spleen. The disease progresses rapidly and terminates fatally in a short time, splenectomy should, therefore, be performed as soon as the diagnosis is made. In *hemolytic icterus* the recovery was complete. In the cases of *sickle-cell anemia* the condition has been little benefited; but the abdominal and joint crises have been alleviated. Results in *hemorrhagic purpura* are nearly as good as in hemolytic icterus. Two cases of early stage *Banti's disease*, seem to have been cured.

#### STOMACH. — CARDIOSPASM.

—In 14 years A. Fromme (Beitr. z. klin. Chir. 162:337, 1935) has treated 24 cases of this condition. He classifies the cases etiologically into 3 groups: (1) those with a psychogenic disturbance of the cardiac innervation without any anatomical change; (2) those in which the condition was due to an organic cause—paralysis or irritation of the nerves—

supplemented by psychic trauma; and (3) those with purely organic disturbances.

In 3 cases with organic changes there were evidences of previous disease of the cervical lymph glands. In 3 others, pulmonary changes of a probable tuberculous nature were found. In 1 case the cardiospasm followed a severe attack of grippe, and in another, the birth of a third child. In 2 cases duodenal ulcer was suspected, and in 3 the condition was attributed to trauma.

The author distinguishes the *type* according to the form of the esophageal dilatation. In one type the enlargement extends all the way to the neck. Fromme attributes this type to a general disturbance of the innervation of the organ. In another type the greatest enlargement occurs in the supracardial part of the esophagus which at first remains straight, but after prolonged stasis above the diaphragm forms a broad sac with its convexity to the right. The latter type is believed to be due to a disturbance of the opening reflex of the cardia.

Of the author's 24 patients, nearly all of whom were subjected to repeated physical and x-ray examinations, 15 were treated surgically. In 1 case **gastrostomy** was done; in 2 cases, an **extramucouscardiotomy by Heller's method**; in 4, **plastic surgery**; and in 8, **gastroesophagoanastomosis by Heyrowsky's method**. The 1 death, which was due to suture insufficiency, followed a Heyrowsky operation. In 5 cases the esophagus was **dilated with Starck sounds**, a method which failed in 2 other cases. Two patients were treated by strictly conservative methods.

The evaluation of the *results of treatment* is difficult because the findings at various follow-up examinations may vary greatly. An important difference between the patients who were operated upon and those who were treated con-

servatively or not treated at all was the fact that those treated surgically were never again troubled by inability to swallow or malnutrition. The best functional and anatomical operative results were obtained by **anastomosis**, although painful spastic conditions were very common in patients so treated. The second best results were obtained by **Heller's operation** and by **dilatation with Starck sounds**. A patient who was not benefited by an operation performed by Heller was operated upon by the author by the transpleural method because it appeared that the Sauerbruch abdominal operation would be difficult. The operation was followed by death from an undetermined cause. Although most surgeons have rejected treatment with Starck sounds, the results in the author's cases in which this method was used (mild and moderately difficult cases) were satisfactory. In some of them, however, repeated dilatations were necessary. Fromme calls attention to the fact, demonstrated also in one of his cases, that considerable improvement of cardiospasm may occur without treatment. The most unfavorable results in his cases were those of **plastic surgery**. On account of the cicatricial changes which are always to be expected at the cardia, he repeats sounding or performs a second operation only after careful consideration.

The *technic of the transabdominal operation* which is preferred by Fromme for the relief of cardiospasm is as follows:

Depending upon the form of the costal arch and the site of the cardia, a medial, hooked, or rib-margin *incision* is made under *anesthesia* of the abdominal wall supplemented by intestinal or inhalation anesthesia. A transverse incision of the peritoneum is then made at the site of the cardia. After displacement of the vagus nerve from the region of the cardia and withdrawal of the esophagus from the diaphragm to an extent of from 6 to 9 cm.,

the esophagus is ligated as far toward the oral cavity as possible with a strip of gauze and the stomach is similarly ligated after the formation of an opening in the lesser omentum and the gastrocolic ligament. Both strips of gauze are then fixed to the stomach and esophagus by a suture, so that the organs are closely approximated. Anastomosis is done in 2 layers with an inner suture of catgut and an outer suture of silk, and the suture line is covered with a flap of peritoneum.

According to G. Lotheissen (Zentralbl. f. Chir. 62:2658 (Nov. 9) 1935), most cases of so-called cardiospasm yield to nonsurgical dilation, for among about 120 cases he found only 2 in which more radical interventions become necessary. In one of these cases he did the **cardioplasty according to von Hacker** and obtained good results. The second patient, a woman aged 52, had a dilatation of the esophagus and a severe cicatricial stenosis (probably the result of ulcerations). It was decided that the stenosis had to be excluded and that a new connection with the stomach had to be formed. After mentioning the shortcomings of the methods usually employed in such cases, the author describes his *new technic* as follows:

The abdominal cavity was opened in the midline. Following division of the peritoneum at the diaphragm, the esophagus could be readily detached and drawn down for about 8 cm. It was then again attached to the diaphragmatic cleft with button sutures. Then the esophagus was again turned back so that the anterior wall was exposed, and an elastic Doyen clamp was put on it directly anterior to the diaphragm. The ectasia had been well irrigated, but in order to make sure that there could be no escape of contents, the surroundings were well covered with compresses. Then the entire constricted portion (4 cm. in length) was incised down to the lumen and the mucous membrane was immediately attached all around to the external wall by means of button sutures; so that, a sort of cardiectomy was made, but intentionally also through the mucous membrane. Then followed the intussusception of the constricted portion into the stomach and the attachment of an anterior

fold, which on both sides was joined to the posterior fold with a double suture, to the dilated esophagus. By this the cut portion was completely buried. In order not to impair the sutures and yet to insure proper nutrition of the greatly weakened and emaciated patient, a gastric fistula was made.

The author points out that since the disorder is always designated as cardiospasm, even if the stenosis is at the diaphragm, his operation can be designated as **cardiodysis** (intussusception of the cardia). He considers that cardiodysis is advisable, especially for cicatricial stenoses. The covering with folds greatly reduces the danger of infection. Considerable dilatation of the esophagus is, of course, a prerequisite for this intervention.

**PYLOROSPASM.**—Theories regarding the etiology of pylorospasm *in childhood* are advanced by K. Eberle (Wien. klin. Wchnschr. 49:845 (July 3) 1936). After describing the symptomatology the author shows that the prolonged vomiting produces, in addition to other disturbances, also a severe metabolic disorder. There is exsiccosis with inspissation of the blood and albuminuria, also chloropenia with achloruria and hypochloremia.

In discussing the *therapy* of pylorospasm, the author says that x-ray treatment has been abandoned. He then mentions the various medicaments that have been tried, such as **papaverine** and **atropine**. The favorable reports of other clinics induced his clinic to try a **scopolamine** preparation. After overcoming the comatose condition by careful treatment with **sodium chloride**, the treatment was continued with sodium chloride and the scopolamine preparation. Under the influence of this treatment the vomiting ceased rapidly. The author states that the new internal treatment of pylorospasm stresses the following point: Pylorospasm should be treated

in a hospital. The food intake should be under strict control. There should be frequent feedings with small concentrated portions. The child should be under the care of a conscientious nurse. The formerly employed gastric irrigations are inadvisable, because they lead to further depletion of the chloride reserves. The loss of chlorides and water is compensated by the **frequent small feedings**. In giving his attention to the surgical treatment of pylorospasm, the author says that the new **Weber-Ramstedt method** is the best. He considers surgery indicated when careful internal treatment fails. Following the operation, feeding must again be carefully supervised, for if this is not done, alimentary intoxication may result.

**PYLORIC HYPERTROPHY.**—*Idiopathic pyloric hypertrophy in adults* is explained by G. S. Donati (Ann. ital. di chir. 14:1145 (Oct.) 1935), who reports 2 cases of pure pyloric hypertrophy in women aged 28 and 40, respectively. The author states that the disease is more frequent in women than in men. From early life the patients show recurrent gastric disturbances, which become intensified as the condition develops. The clinical diagnosis, especially of atypical benign forms, is difficult. When the disease is already developed, the clinical symptoms and objective and x-ray signs are those of pyloric stenosis due to ulcer. The anatomic lesion involves the muscular layers of the pylorus without involving the layers of the gastric wall. Pure pyloric hypertrophy is entirely different from inflammatory and sclerous, neoplastic and myomatous forms of pyloric hypertrophy. It is equivalent in adults to pyloric hypertrophy in infants. Certain zones around the pylorus are more intensely involved than others in the pure hypertrophic process. Both congenital and acquired factors, especially

those related to the production of pyloric spasm, are involved in the pathogenesis. The treatment is surgical, especially in grave cases complicated by emaciation. The rather frequent finding of the condition at necropsy proves that the disease is not as rare as has been believed.

#### **VOLVULUS OF STOMACH.—**

After reviewing the history of volvulus of the stomach, N. Anagnostidis (Rev. de chir. Paris 73:515 (July) 1935) reports a case of the condition. In this case the spleen, which was very large, was found in the right lower quadrant of the abdomen and the stomach was rotated 180° from left to right. Along the lesser curvature of the stomach there was a gangrenous area. The spleen was removed, the stomach rotated back into place, and the gangrenous area resected. The patient died 8 hours later.

In the literature the author has been able to find reports of 116 cases of volvulus of the stomach, 63 of the subjects being women. The incidence of the condition was highest (28 per cent.) between the ages of 41 and 50 years.

All or only a part of the stomach may be rotated. Partial torsion involves only the pyloric end. The torsion may be: (1) around the axis from the pylorus to the cardia, the so-called organoaxial or pylorocardiac volvulus; (2) around the axis from the greater to the lesser curvature, the so-called mesentericoaxial volvulus or volvulus on the axis of the lesser curvature; or (3) of a mixed type. Of 108 cases in which the volvulus was described in detail, it was of the organoaxial type in 57 (52.7 per cent.); of the mesentericoaxial type in 45 (41.6 per cent.); and of the mixed type in 6 (5.5 per cent.).

In the organoaxial type the greater curvature may turn forward and upward. When the torsion reaches 180° the posterior wall of the stomach comes into contact with the anterior abdominal

wall. This is called an "anterior" or "isoperistaltic" volvulus. Less frequently, the torsion is in the opposite direction, a "posterior," "antiperistaltic" or "anisoperistaltic" volvulus. In the mesentericoaxial volvulus the pylorus usually moves forward and to the left, while the cardia moves posteriorly and to the right. Less frequently, the pylorus moves posteriorly and to the left, and the cardia forward and to the right.

Volvulus of the stomach is associated with occlusion of the orifices of the stomach, venous congestion, distention of the organ, a serosanguinous peritoneal exudate, and occasionally, gangrene and perforation.

The *etiology* is not clear. In 43.9 per cent. of the 116 cases recorded in the literature the condition was described as idiopathic. Predisposing factors are a rapid loss of weight with relaxation of the abdominal wall, nervousness, pregnancy, gastric atony, congenital or acquired abnormal mobility of the stomach and colon, inflammatory adhesions, diaphragmatic hernia, gastric neoplasms and ulcers, and displacements of neighboring organs.

*Symptomatically*, the condition may be classified as acute, chronic, or intermittent. Acute volvulus is associated with the following signs and symptoms: (1) a desire to vomit without being able to do so; (2) gaseous distention limited to the gastric area; and (3) the impossibility of passing an esophageal sound or a stomach tube into the stomach. The condition occurs suddenly, with intense pain localized in the epigastrium. As a rule, it is accompanied by elevation of the diaphragm, displacement of the heart, dyspnea, and signs of shock.

*Chronic volvulus* is usually partial, involving only the pyloric end of the stomach. The symptoms are those of long-continued indigestion suggestive of ulcer, gastritis, or carcinoma.

In the *intermittent type* of gastric volvulus the clinical picture consists of a series of attacks similar to, but less intense than, those occurring in the ordinary acute type.

The *diagnosis* is usually easy if the condition is borne in mind. The *treatment* is surgical.

**PROLAPSE OF GASTRIC MUCOSA.**—Prolapsing lesions of the gastric mucosa are described by E. P. Pendergrass and J. R. Andrews (Am. J. Roentgenol. 34:337 (Sept.) 1935), who call attention to the lack of a characteristic clinical syndrome. For preoperative recognition of the condition, x-ray examination is of prime importance. The findings of roentgenoscopy are far more reliable than those of roentgenography.

The essential *diagnostic* feature from the x-ray standpoint is a large negative filling defect of the pyloric end of the stomach which is movable and can be pushed into the duodenum, where it produces a deformity of the cap. Gastric stasis and fixed pyloric or duodenal defects may or may not be present. The peristalsis and motility vary considerably in different cases and their variations are not dependable evidence of the presence of prolapsing lesions of the mucosa. No reliable criteria for differentiating between prolapsing gastric polypi and prolapsing hypertrophic gastric mucosa have been established as yet.

The errors in the diagnosis of prolapsing lesions of the gastric mucosa are due, not to mistaking these lesions for others, but to mistaking other lesions for these lesions. In the *differential diagnosis*, congenital mesenteric membranes, redundant normal membranes, inflammatory adhesions, a hypertrophic pyloric muscle, and duodenal and gastric ulcers, gastric carcinoma, and retained food particles must be ruled out.

In conclusion, it is stated that when a suggestive appearance is observed in

the roentgenogram in the presence of negative x-ray findings, the diagnosis of a prolapsing lesion of the gastric mucosa should be held to be equivocal and the patient reëxamined with special attention to the findings of roentgenoscopy.

**BENIGN TUMORS OF STOMACH.**—The occurrence of *gastric polyposis*, according to E. M. Van Buskirk (J. Indiana M. A. 29:218 (May) 1936), is relatively infrequent. The *etiology* is not definitely known. The condition is often found in association with hypertensive cardiovascular disease, syphilis, tuberculosis, chronic pleurisy and atheroma of the vessels. The microscopic picture consists of hypertrophied gastric glands and varying stages of vascular congestion involving only the mucosa in general, the musculature and the connective tissue being free. Grossly, the tumors are more or less uniform, being soft in consistency and gray, grayish brown or red, depending on the vascularity. They may vary in size from millet seeds to covering the major portion of the stomach. The surface of the tumors may be covered with a thick, egg-white mucus or hemorrhagic areas of ulceration. At times, inspection of the stomach will not be very enlightening, but palpation may give the sensation of the presence of food.

That the *symptoms* of gastric polyposis are not characteristic is revealed by the fact that they are unexpectedly found at necropsy or at operation. At times, the duration of symptoms covers a period of years and then occasionally may be very brief, with anemia, loss of weight and strength being the apparent sole manifestations. In some cases a sense of pressure or weight in the epigastrium, progressing to discomfort and abdominal distress, and in other cases abdominal pain are usually the most

common complaints. The physical observations are practically negative. The most important procedures revealing conclusive evidence consist of fluoroscopy, x-ray and gastroscopy.

In making a *diagnosis* of gastric polyposis, all factors must be considered and all possibilities must be utilized.

In the *differential diagnosis* of gastric polyposis, carcinoma, extragastric tumors, foreign bodies, hairballs, ulcer, pernicious anemia, functional dyspepsia, sarcoma and syphilis should be considered; but any of these conditions may be present coincidentally with gastric polyposis. In all cases careful x-ray examination with accurate interpretation offers the greatest aid in diagnosis.

Carcinoma is sometimes found in conjunction with gastric polyposis, one portion of the tumor being benign and the other part undergoing malignant degeneration. Cases with stenosis of the pylorus or obstruction of the pylorus, due to a polyp of the stomach; intermittent stenosis of the pylorus, due to a gastric polyp; intussusception into the stomach and duodenum, due to a gastric polyp and hemorrhage, have been reported as *complications*.

**Surgical and adequate reconstructive procedures** are indicated in the individual cases and often have changed a diagnosis of malignant tumor to one of benign tumor and given the patient years of good health. When surgical removal is impossible, **x-ray therapy** and **radium** may prove beneficial.

H. N. Comando (Arch. Surg. 30:228 (Feb.) 1935) points out that *Hodgkin's disease* may originate in the lymphoid tissue of the gastrointestinal tract and remain as a localized tumor for some time. The diagnosis usually made is that of carcinoma. Before the days when gastric resection was the operation of choice for gastric tumors and for infiltrating gastric ulcers, virtually no cases

similar to the one the author describes were reported in the literature. This type of gastric lesion is a distinct clinical entity, and the favorable results that have followed operative treatment in several cases more than justify the **radical operation**. The *pathologic changes* noted in his case were those of an infiltration of the distal portion of the pars media and the proximal part of the pyloric portion of the stomach. A Wassermann test was advised, in order to rule out syphilis, before an interpretation of the condition as a malignant process was accepted. An increased density was noted in the region of the liver. A small deposit was noted in the lower lobe of the left lung. The patient left the operating room in good condition and made an uneventful recovery. In two months he had gained 25 pounds (11.3 Kg.), had returned to his usual occupation, and was able to eat all kinds of food. A careful follow-up has shown no evidence of any recurrence and the patient continues to feel well.

**MALIGNANT TUMORS OF STOMACH. — Pathogenesis.** — The beginnings of gastric cancer are discussed by J. Ewing (Am. J. Surg. 31: 204 (Feb.) 1936). The author observed a case of early superficial *adenocarcinoma* arising at multiple points over a rather wide area of hyperplastic gastritis. If this condition had progressed, it would probably have resulted in a large region of superficial erosion with gradual extension of the disease through all of the coats of the stomach. Ewing suspects that this is the mode of origin of many of the superficial erosive carcinomas of the pyloric antrum in which there is no localized tumor or ulcer, and only a diffuse erosion of the mucosa and infiltration of the submucosa are found. He says that the gastritis is not the usual chronic hypertrophic form, with greatly

enlarged glands and increased stroma, but one which is highly atypical from the first and changes into cancer rapidly. It suggests the local action of a strongly cancerogenic irritant.

The early literature on gastric cancer shows that the development of adenocarcinoma from multiple foci has frequently been observed and usually occurs from rather well-defined areas with fully developed but small adenocarcinomas separated by normal mucosa. In the case reported by the author there were diffuse atypical changes over the entire affected region without any normal mucosa.

Both of these processes, especially the latter, probably lead in later stages to the wide superficial ulcerating adenocarcinomas found occasionally.

Other ways in which superficial erosive carcinomas begin are known. There is a group of cases in which the superficial epithelium and the epithelium of the ducts remain intact, but the tubular gland fundi break up and the malignant epithelial cells infiltrate widely over the mucosa.

Congenital or acquired structural abnormalities give rise to a small proportion of gastric cancers. Heterotopic intestinal mucosa is frequently found in the pyloric region, and some investigators have traced ulcers and cancers to this origin. Pancreatic islands found in the stomach wall must be considered rare sources of peculiar types of carcinoma. Misplaced islands of gastric glands may be found in the stomach wall.

Carcinoma arising in the ordinary type of chronic hypertrophic gastritis seems to be rare. In the polypoid form of chronic gastritis, single or multiple carcinomas are frequent.

These observations on early gastric cancer have a bearing on *ulcerocancer*. It appears that adenocarcinomas tend to

ulcerate at a very early stage. Therefore, the presence of islands of cancer in the edges of an ulcer is no indication that the cancer is the sequela of the ulcer.

The occurrence of multiple areas of early cancer in a localized area also complicates the interpretation of cancerous ulcers. If an adenocarcinoma extends laterally by ulceration, it may encounter in its advance a second or third focus of primary carcinoma. Segments of the ulcer will then show points of carcinoma developing through gradual transformation of the glands on the edge of the ulcer. These secondary cancers will have no relationship to the original cancer or ulcer. They are primary independent cancers.

**Symptomatology and Diagnosis.**—S. Harris (*Ibid.* 31:225 (Feb.) 1936) points out that before the diagnosis of gastric cancer will be made early enough for much hope of cure from surgery, most of the articles on ventricular carcinoma in the textbooks on medicine available to the general practitioner will have to be rewritten. The symptoms making up the generally accepted criteria for the diagnosis of cancer of the stomach, *i. e.*, abdominal pain, nausea, vomiting, emaciation and anemia (cachexia), are late manifestations due to ulceration, secondary infection and obstruction; and, when they occur, in the majority of cases the patient has lost his chance for a cure by surgery or any other method of treatment. The earliest manifestation of gastric cancer in an individual more than 30 years of age, who is otherwise healthy, usually is what he calls "just a little indigestion." If such a person, as soon as he becomes stomach conscious, will consult the most capable gastroenterologist or internist available, who will take time for a thorough study of his case, including x-ray examination by an expert roentgenolo-



gist, the diagnosis may be made early enough for the patient to be cured by an operation. In a small proportion of cases cancer of the stomach becomes engrafted on gastric ulcer, though it is extremely rare for a duodenal ulcer to become malignant. Therefore, if the individual who has an ulcer of the stomach is not speedily relieved of symptoms, or if there is a recurrence of symptoms after rest and dietary management for a few weeks in a hospital under a capable and experienced clinician, he should have an operation with the hope of removing the precancerous ulcer before it becomes malignant. The annual or semiannual physical examination may reveal symptoms that would cause the well informed physician to suspect cancer of the stomach earlier than now is being done. Therefore, if the public can be taught the need for the annual or semiannual physical examination by capable physicians, there is hope of decreasing the present high death rate from cancer of the stomach.

In cases of gastric cancer, the *x-ray* findings discussed with the surgeon should be used in determining not only whether operation is indicated, but also choosing the type of operation to be performed. Complete knowledge of the region of the stomach involved and of the extent and type of the lesion may lead the surgeon to abandon his usual procedure and perform an operation of another type.

L. G. Cole (*Ibid.* 31:206 (Feb.) 1936) states that the *x-ray* findings may be used for a practical clinicopathological classification for guidance in determining the treatment and the solving of other cancer problems. The author recommends the following classification based on 4 roentgenopathological characteristics:

1. Regional characteristics: the distance of the proximal line of invasion

from the pylorus: (a) antral or pyloric; (b) corporeal; (c) cardiac; and (d) fundic.

2. Obstructive characteristics: the protrusion of the growth into the lumen of the stomach: (a) obstructive; (b) nonobstructive.

3. Infiltrative characteristics: (a) infiltrative; (b) noninfiltrative.

4. Protruding characteristics: the character of the protrusion of the growth into the lumen of the stomach and its surface characteristics: (a) protruding; (b) nonprotruding.

Cole states that all of these x-ray findings are practically identical with the gross pathological changes.

The great majority of the malignant tumors of the stomach are carcinomas. The occurrence of lymphosarcoma, fibrosarcoma, myosarcoma, and neurosarcoma in the stomach is very rare.

G. T. Pack and G. McNeer (*Ann. Surg.* 101:1206 (May) 1935) report 9 cases of *sarcoma* of the stomach which included 4 of *myosarcoma*, 3 of primary gastric *lymphosarcoma*, and 2 of generalized *lymphosarcomatosis* with secondary involvement of the stomach.

The sarcomas constitute about 1 per cent. of all gastric tumors. They occur with equal frequency in males and females. The average duration of the symptoms is 9½ months. As a rule, it is impossible to differentiate a sarcoma from a carcinoma of the stomach by x-ray examination, but horizontal filling defects and the persistence of gastric peristalsis in the presence of a definite lesion suggest the former.

The *treatment* of choice for localized tumors is **partial gastrectomy**. This is especially effective in the cases of exogastric *sarcomas*. Gastric *lymphosarcomas* are extremely radiosensitive and usually respond favorably to well-planned **irradiation treatment**.

LABORATORY DATA.—In 75 cases of gastric cancer, E. Mogensen (Hospitalstid. 79:85 (Jan. 28) 1936) states that the average percentage of hemoglobin was 72.8. In 31 per cent. of the cases there was no anemia and he concludes that the presence of a normal percentage of hemoglobin is without significance in the diagnosis of cancer of the stomach. No connection existed between achylia and tendency to anemia or between the degree of occult hemorrhage and anemia, and the anemia was independent of age, sex and duration of the disease. Undernutrition and cessation of the antianemic function of the stomach are regarded as the main causes of the anemia. Two cases of cancer of the stomach with marked anemia as the chief symptom are described, one with a hypochromatic and microcytic anemia which responded favorably to treatment with **iron**, the other with a hyperchromatic megalocytic anemia which reacted well to treatment with **liver and stomach**. The importance is stressed of active treatment of the *anemia* in cancer of the stomach by (1) the **best possible nutrition**, both quantitatively and qualitatively, and (2) direct antianemic treatment with **iron** or with **liver and stomach** or both, the choice being based on the hematologic picture.

The blood platelets were counted in 18 patients suffering from gastric cancer by V. A. Franco (Prensa méd. argent. 23:977 (Apr. 15) 1936). In all the cases the number of platelets per cubic millimeter of blood was normal. The clinical diagnosis of gastric cancer was confirmed in all cases by the evolution of the disease and by the performance of either an operation or a necropsy. On the basis of his results and of the fact that thrombocytopenia is a constant blood alteration in patients suffering from pernicious anemia, the author ascribes value to the counting of platelets

in the *differential diagnosis* of pernicious anemia and gastric cancer and advises further work in this field for verification of his statement.

**Treatment.**—According to W. Walters (Minnesota Med. 19:91 (Feb.) 1936), the proper treatment for *carcinoma* of the stomach is **surgical removal** whenever possible. Every patient who has cancer of the stomach, regardless of how extensive, should be allowed the benefit of surgical exploration of the lesion, provided distant metastasis is not demonstrable. In from 10 to 15 per cent. of those cases in which the lesion, on x-ray examination, appears to be inoperable because of its extent, surgical removal of the lesion can be accomplished. Large malignant lesions of the stomach will often be found to be of a low degree of malignancy, to be sharply demarcated and to present no involvement of lymph nodes. Removal of such lesions by **partial gastrectomy** gives a high incidence of permanent cure and this is particularly true in elderly patients. At the Mayo Clinic the finding of an extensive carcinoma, localized in the stomach, or even of one associated with involvement of lymph nodes, is viewed from the standpoint that, unless the lesion is removed, the patient is doomed to early death. In several cases **total gastrectomy** has been performed successfully at the clinic, and patients have lived and been comfortable 2 and 3 years subsequently. That such an operative procedure can be carried out in suitable cases with great benefit to the patient has led to the impression that all gastric lesions should be removed unless they have invaded adjacent structures to the extent that the carcinomatous process cannot be removed in its entirety. It is not an uncommon experience to find that a growth which is examined while the patient is straining under light anesthesia appears to be unremovable but under

deep anesthesia may be seen to be readily removable. It is not the age of the patient, but his general condition that is a factor in the surgical mortality.

The author has found it of value to approach all extensive lesions of the stomach through a left rectus *incision*, as suggested by Balfour. In general, a **posterior Polya** or an **anterior Polya-Balfour** type of anastomosis is the most satisfactory type of reconstruction

stricted to assist in healing of the anastomosis. This is of particular value for patients who have lost a considerable amount of weight and who have been debilitated as a result of carcinomatous obstruction. The presence of abnormal gastric lesions from 1 to 1.5 cm. in diameter can be detected by a competent roentgenologist. Many small lesions of the stomach, which appear to be benign on x-ray examination and even at the

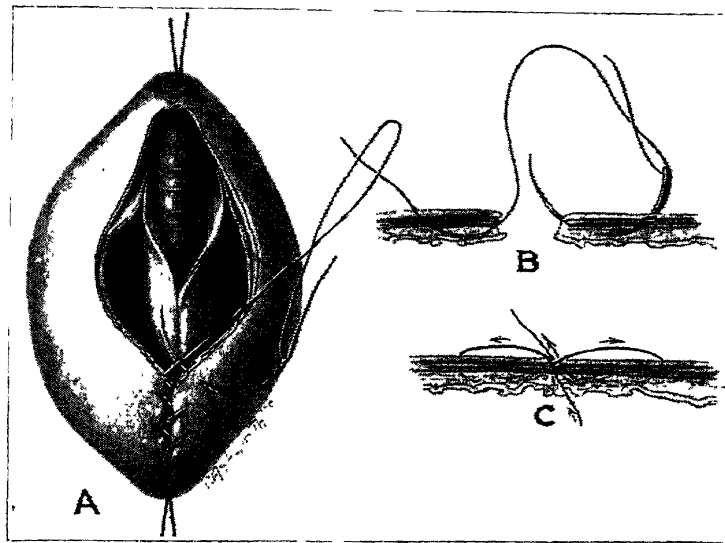


Fig. 8.—A. The authors' two-layer serosomucosal suture used anteriorly with an ordinary serosubmucosal suture used posteriorly; the mucosa not being sutured. B and C. Cross-section of the authors' suture. The anterior suture layer in A is drawn up more closely than is illustrated in A and C so as to cause serosal inversion. It is reinforced by a layer of Halsted mattress sutures which are not shown in illustration. (Martzloff and Suckow: Arch. Surg.)

following extensive gastric **resection** for malignant disease. However, in certain instances the original **method of Billroth**, in which the stomach and duodenum are anastomosed, has worked out to advantage, although the greatest field of its applicability is in the presence of benign gastric ulcers, bleeding duodenal ulcers and recurring ulcers.

When extensive gastric resections have been performed on elderly patients, particularly in the case of subtotal or total gastrectomy, **jejunostomy** as a means of providing a temporary method of feeding has a decided advantage. During this time oral administration of fluids is re-

stricted to assist in healing of the anastomosis. This is of particular value for patients who have lost a considerable amount of weight and who have been debilitated as a result of carcinomatous obstruction.

**TECHNIC IN GASTRIC SURGERY.**—The results obtained by K. H. Martzloff and G. R. Suckow (Arch. Surg. 31:10 (July) 1935) in experiments on 20 dogs confirm their previous observation that suture methods which tend to evert the mucosa into the line of apposition in gastrointestinal anastomoses cause mucosal inclusions with appreciable frequency. These inclusions persist, as they were found 90 days after the operation, and when they do not establish a communication with the gastrointestinal lumen, they may form cysts of consider-

able size. In some specimens these inclusions were accompanied by inflammatory phenomena after a 90-day period of healing, whereas anastomoses not complicated by mucosal eversion showed almost complete absence of inflammatory phenomena after a healing period of 20 days or less.

The authors describe a simple and practical 2-layer anterior suture method which avoids eversion of the mucosa and trauma to the mucosal margins and at the same time controls capillary oozing and permits rapid and uncomplicated healing.

This procedure, which they have not seen described before, is a 2-layer **serosubmucosal suture** (Fig. 8). The catgut suture (No. 00 plain) used posteriorly as the innermost layer is continued anteriorly as the innermost anterior layer to unite the stomach and intestine. The suture is carried on a fine curved or straight intestinal needle which is always directed obliquely toward the cut edge of the opening and in the direction of the unsutured defect. The needle is introduced about 0.5 cm. from the cut edge of the viscus and penetrates only to the outermost layers of the submucosa. It is brought out at the cut edge of the viscus so that it pierces the muscularis and avoids the cut edge of the mucosa. When the suture is tensed, it brings the cut edges of stomach and intestine together, as shown in the illustration. Further tension inverts the serosa, and still further inversion is effected by a row of Halsted silk mattress sutures which complete the procedure. For the posterior suture, the method is impracticable because it does not produce sufficient hemostasis and is difficult to place accurately. For this stage of the anastomosis the usual through-and-through circular suture or the lockstitch is recommended, as these do not cause the undesirable complications that may occur in the anterior suture.

The authors' previous observations with regard to the use of **silk suture material** in gastroenterostomy were also confirmed by the findings of the experiments reported in this article. It was found that when silk sutures are so placed that they do not penetrate the mucosa, they are ideal, as the inflamma-

tory reaction they produce is minimal; whereas, if they penetrate the intestinal mucosa, as they occasionally do even when introduced with care, they become complicated by infection and inflammation and often by mucosal inclusions, all of which may persist for 90 days or longer. The authors therefore doubt the advisability of using silk suture material in gastrointestinal anastomosis.

Some points in the operation of **gastrectomy** are outlined by W. H. Ogilvie (Brit. M. J. 1: 457 (Mar. 9) 1935). The purpose of this article is to analyze the *dangers and functional failures* of gastrectomy and to suggest measures by which they may be avoided.

Deaths following gastrectomy are usually due to shock, hemorrhage, peritonitis, or postoperative pulmonary complications. Surgical shock is due to prolonged handling, protracted anesthesia, and loss of blood. It may be combated by more adequate exposure of the upper part of the stomach and the first part of the duodenum; a better understanding of the anatomical planes dissected; and diminution of the number of bleeding vessels to be tied by reduction of the length of the cut surfaces to be approximated by suture. The most important requisite is simplification of the operation.

The *functional failures* of gastrectomy may be classified into 3 main groups: (1) recurrent ulceration; (2) postoperative discomfort; and (3) anemia. As the dangers, difficulties, and failures are closely related, the author discusses them together to avoid repetition.

With the possible exception of nitrous oxide, all anesthetics are, to a varying degree, tissue poisons which administered in sufficient concentration for a sufficient time, may alone cause shock and in combination with prolonged tissue handling are certain to have such an effect. It is, therefore, desirable to *avoid general*

*anesthesia.* Spinal anesthesia at the level of the diaphragm is uncertain and has too profound an effect on the blood-pressure to be safe. There remains, therefore, only **local anesthesia**, either alone or in combination with the use of **nitrous oxide** and **oxygen**. Following proper **premedication** and **splanchnic infiltration**, pain is entirely abolished, relaxation of the abdominal walls is complete, respiratory movements are slow and shallow, the blood-pressure is not elevated, and the capillaries are not dilated. By splanchnic infiltration the technical phase of the surgery is so remarkably simplified that any surgeon is able to save the 20 minutes required for the injection of the anesthetic. In the postoperative stage following local anesthesia the patient is able to take fluids by mouth immediately.

Access is most difficult and accuracy most essential for high gastrectomy in the neighborhood of the left gastric artery, at the cardiac end of the lesser curvature, and at the duodenum. A median *incision* is recommended. There never is any necessity to go below the umbilicus, but the incision may be prolonged upward to the level of the xiphisternum and may there extend 2 inches above the perimedian approach.

On the basis of the embryological development of the great omentum and the absence of anastomoses between the omental blood vessels and the colon, the author recommends that the omentum and colon be separated by running a knife along the bloodless plane between them which is close to the colon. This opens the old plane of adhesions and renders it easy to separate down to the posterior abdominal wall, restoring the fetal condition. When this is done correctly, ligatures are required only at both ends of the gastroepiploic arch, *i. e.*, one at the origin of the right vessel from the gastroduodenal artery and the other near the spleen. For preservation of an adequate circulation for the omentum, the omentum should be separated proximal (gastral) to the gastroepiploic arch. The common technic of gastrectomy in which the vessels of the omentum are tied 2 inches from the gastric curvature is anatomically

wrong and technically a waste of time. It is wrong because division of these vessels cuts off the entire omental blood supply, rendering the omentum a bloodless fat graft destined to become fibrous and promote adhesions.

Ogilvie has *simplified* his *technic of gastrectomy* by avoiding the duodenum, which is one of the chief hazards of abdominal surgery. He states that the duodenum has many dangers peculiar to itself. It has a large, thick, and pliable muscular wall which is difficult to suture and infold. It has a very abundant supply of blood vessels, the most troublesome of which are those from the pancreas. Ogilvie has found that after the duodenum is separated from the pancreas for about  $\frac{3}{4}$  inch a simple purse string suture is safe without the row of infolding sutures usually recommended. He crushes the duodenum at the point selected for division, ties it firmly with a silk ligature in the crushed groove, introduces a purse string suture on the pancreatic side and laterally, and then ties over this purse string suture a second purse string suture which includes the cut tip of the peritoneum on the head of the pancreas.

He states that if access of acid gastric juice is entirely and permanently prevented by division of the pyloric end of the stomach, a duodenal ulcer will heal and remain healed. Transverse division of the stomach 2 inches proximal to the pylorus is, therefore, quite as efficacious in gastrectomy for ulcer as the usual duodenal occlusion. In both **resection** for cancer and for ulcer the removal of the stomach must be thorough. At least three-fourths of the stomach must be resected. In this resection the left gastric or coronary artery should be ligated. The right gastric or pyloric artery may be ignored as a textbook mythical structure. Ogilvie prefers **Finsterer's modification of the Polya resection**. In this procedure the opening in the gastric fragment remaining after resection is closed, beginning at the lesser curvature, by 2 or more rows of sutures, so that the infolded line extends nearly to the cardia. The jejunum is anastomosed to the remaining half of the opening, the distal loop is anastomosed to the greater curvature, and the proximal jejunum is later sutured to the closed part of the stomach. In this manner the suture line is reinforced and a thick valve of gastric and jejunal wall is interposed between the gastric outlet and the proximal loop. Regurgitation into the duodenum is, therefore, effectively controlled.

The *common causes of failure of gastrectomy*—postoperative vomiting, postprandial discomfort, and proximal loop distention—have already been combated by the described Finsterer gastrectomy. Recurrent ulcers can develop only if the postoperative acid level remains high, as may be the case when the resection has been too conservative.

Recent study suggests that the *anemia following gastrectomy* has no relation to the amount of stomach resected, but is dependent upon the functional disturbance produced by the operation. An equally severe anemia may follow gastroenterostomy. In the absence of gastrointestinal disturbances, the anemia associated with gastrectomy responds readily to the administration of **iron and ammonium citrate** by mouth.

In 140 patients followed by Ogilvie after gastrectomy no change was found in the blood picture.

**Postoperative Treatment and Complications.**—**PREVENTION OF GAS PAINS.**—L. E. Mahoney (Am. J. Surg. 32:272 (May) 1936) believes that the further step to be taken to minimize abdominal postoperative discomfort is a general solid **diet**, with modifications necessitated by different temperaments and varying conditions. The human intestinal tract is a muscular tube the mucous membrane of which secretes digestive ferments and the motility of which is largely dependent on these ferments and the presence and character of the food material in the intestine. Activity of the liver, the chemical engine of the body, and the secretion of bile is greatly influenced by the amount and the variety of ingested food. Whenever starvation supervenes, and the usual hospital liquid diet is really semistarvation, the bacteria normally present in the intestine increases enormously and produce large amounts of flatus. If lack of the food to which the upper intestine is

accustomed continues for more than a very few hours, those species of bacteria normally resident in the colon and cecum ascend into the ileum and jejunum and there proliferate, giving rise to huge amounts of gas and to symptoms of toxemia from absorption.

Practically all successful medical treatments for colonic stasis appear to depend for their efficacy on lowering or modifying the bacterial content of the colon. The factors in health and normal well-being that keep down the growth of these organisms are bile, the hydrochloric acid of the stomach, and the digestive ferments, powerfully aided by the peristaltic action of the intestine, which endeavors to move the food taken in by mouth as far as the ileocecal valve in about 6 hours or less. Necessarily, if starvation or semistarvation is added in the form of the usual hospital "liquid diet" to the systemic shock of an abdominal operation, the secretion of hydrochloric acid, bile and the digestive ferments is decreased, or perhaps these activities are altogether abolished temporarily, and in addition peristaltic action is greatly diminished, thus the multiplication of putrefactive and gas-producing organisms is favored and everything possible is done to produce abdominal distention in the mild case and adynamic ileus in the severe one.

Patients are urged to eat **solid food** soon after operation, usually the next morning. If not nauseated, they are served a tray the evening of the operative day and encouraged to partake of dry toast, jello, cream of wheat and similar articles. Water is permitted by mouth in such amounts as the patient may desire as soon as the nausea has disappeared. By permitting the **early ingestion of water**, forcing the feeding of solid food, and adding to the feces a bulky ingredient which possesses lubricating properties, other beneficial

side-effects are obtained. Loss of weight is diminished and the fear of the insertion of the needle for administering fluids is abolished.

The prevention of *postoperative distention* is discussed by W. R. Levis and E. L. Axelman (*Ibid.* 32:308 (May) 1936). In reviewing their 88 cases, which form the basis of their report, the authors find that dimethyl carbamic ester of oxyphenyl-trimethyl ammonium methyl sulphate (**prostigmine**) prophylactic, has been most valuable in combating the much dreaded symptoms of postoperative distention and gas pains. In comparing these case records with an analogous series prior to their use of the prophylactic, they have found that distention and gas pains have been reduced to a negligible minimum. Prior to its use, fully 60 to 75 per cent. of their cases would show either subjective symptoms of gas pain or objective signs of gastrointestinal atony or both. Prior to the use of this product the glandular preparations were generally employed, but the results were not sufficiently uniform to warrant continuation of their use. With inhalation anesthetics, the first injection of the prophylactic is given from 3 to 4 hours after operation, followed by a second injection 4 hours later; 4 injections are given at intervals of 4 hours the first day after operation. The last dose is followed immediately by a low soapsuds enema. This technic has proved effective in preventing postoperative intestinal atony. Most gratifying to the patient and the nurse, as well as the surgeon, is the elimination of repeated high compound enemas for the relief of this painful and annoying condition. With this method of administering the prophylactic, peristalsis has been established within 24 hours after operation, whereas prior to its use in abdominal cases peristalsis was not established until after a period of 48 and in some cases

72 hours. Its use has not been attended by any untoward effects by way of systemic or local reaction, the blood-pressure is not affected and cardiac action is not interrupted in any way.

The grave syndrome of *hyperazotemia* and *hypochloridemia* which follows *gastric resection* in gastric or duodenal ulcers, and which, without any other complications may result fatally, is due to alterations of the liver and kidney originating in the absorption of stagnant toxic gastric content by the intestine. C. Antonucci (Policlinico (sez. prat.) 43:427 (Mar. 9) 1936) points out that the gastric content, a mixture of gastric and duodenal secretions, blood and waste material (particles of necrotic gastric and intestinal mucosæ), is secreted and accumulates rapidly after resection, regardless of the technic used, and is highly toxic. Intravenous injections of filtrates of the gastric content, from 2 to 8 c.c. in rabbits, resulted in death of the animals within 1 minute to 48 hours after the injection. In all the animals there was a marked increase of azotemia and a moderate diminution of chloridemia. The parenchyma of the liver and the kidney were congested and greatly injured. The author believes that the results of his experiments support his opinion on the etiopathogenic rôle assumed by stagnation and intestinal absorption of toxic gastric secretions in the development and evolution of the grave humoral syndrome that follows gastric resection. He points out the advisability of performing aspirations of the gastric content 6 hours after gastric resection and then once or twice more the next day, a practice which he carries out systematically in all his cases with satisfactory results. His advice is based on the experience of more than 300 gastric resections in gastric or duodenal ulcers.

That postoperative disturbances represent a difficult problem in gastric surgery

is shown by T. Straaten and M. Hünermann (Med. Klin. 32:562 (Apr. 24) 1936). Investigations in recent years disclosed that the *blood sugar* conditions play an important part. The disturbances in the blood sugar curve after oral sugar tolerance tests throw more light on the estimation of postoperative disturbances after gastric resection. The authors decided to investigate to what extent the changed carbohydrate metabolism and particularly hypoglycemic conditions are responsible for the postoperative difficulties after operations on the stomach. They describe their observations in the course of sugar tolerance tests on 48 patients. They found that the hypoglycemic reaction after sugar consumption is not a reaction that is specific for the stomach that has been operated on. It occurs in patients who have undergone gastric operations, in patients with ulcer or gastritis, who have not been subjected to surgery, and in other diseases, particularly during the period of convalescence. The authors discuss the causes of the *alimentary hypoglycemia* in patients with gastric diseases and in those having undergone surgical interventions on the stomach. They believe that vagotonia, the condition during convalescence, and especially the changed resorption mechanism are responsible. The mechanism of resorption may be altered in gastritis, duodenitis, and jejunitis and because of changes in evacuation. They say that the individual hypoglycemic attack can be counteracted by the administration of **dextrose**. The predisposition to hypoglycemia is best influenced by **frequent small meals** and by not onesidedly preferring carbohydrates. The use of a **special surgical technic** to produce evacuation mechanisms that resemble the normal ones will prevent the hypoglycemic reaction in many cases.

**GASTRIC AND DUODENAL ULCER.**—*Etiology.*—After reviewing the previously reported studies of Vaughn and Dragstedt on the resistance to digestion of various normal organs sutured into large openings in the stomachs of dogs, L. R. Dragstedt (Ann. Surg. 102:563 (Oct.) 1935) reports new experiments which demonstrate that undiluted pure gastric juice will digest these organs.

In 2 dogs a large Pavlov accessory pouch was made of approximately two-thirds of the entire fundus. The pouch was connected to the exterior by means of a tightly fitting metal cannula. Gastric juice could be retained or permitted to escape at will. The spleen was sutured carefully into a large window made in the accessory stomach. During the first week or two the gastric juice secreted in the pouch was promptly drained. During this time it remained fairly clear and the condition of the animals was excellent. Retention of the gastric juice in the pouch for daily periods of 3 or 4 hours was made possible by screwing the cap of the cannula closed. The accumulation of sufficient secretion of the pouch to permit mechanical damage to the implant was carefully avoided. After a few days, gastric juice drainage from the pouch became blood-tinged and severe hemorrhage occurred. The dogs became markedly weak and cachectic. The specimens obtained showed extensive digestion of the spleen by the pure gastric juice, in striking contrast to the almost complete absence of such digestion by the normal gastric contents.

In another series of experiments an isolated gastric pouch was drained into the jejunum and ileum. Of 6 animals in which the (pure) gastric juice passed into the ileum, an ulcer developed in the adjacent area in all, and of 13 animals in which it passed into the jejunum, such an ulcer developed in 11 (85 per



cent.). The ulcers always developed in the intestinal wall adjacent to the line of anastomosis with the gastric pouch. They never occurred in the gastric mucosa.

In a third series of animals the entire stomach was isolated with preservation of its vagus innervation. Observation of these animals demonstrated that if the pure gastric juice was permitted to accumulate in the isolated stomach or if drainage to the exterior was inadequate, ulcers developed in the gastric mucosa.

These experimental observations led to the conclusion that pure gastric juice can digest away living tissue, including the mucosa of the digestive tube.

An attempt was made next to determine what *component of gastric secretion* was *responsible for the digestive effect*. This study was limited to the pepsin and free hydrochloric acid. Hind legs of frogs immersed in pure gastric juice were markedly digested in a few hours. Pancreatic juice had practically no digestive activity, whereas juice with a concentration of 50 units of free acid had a very marked effect almost irrespective of the pepsin concentration. Under normal conditions of motility the gastric content passes into the duodenum before its capacity to bind or neutralize the free hydrochloric acid is entirely overcome, but when there is an abnormal retention, the continuing secretion of gastric juice gradually raises the acidity of the gastric content until it approaches that of the pure secretion.

Spasm of the pylorus would prevent reflux of bile and pancreatic juice which also occurs normally and serves to prevent the development of high concentrations of acid in the gastric content. Should this spasm be associated with a stenosing duodenal ulcer, there would be limitation of regurgitation as well as exaggeration of retention. Then there

would be set up a vicious circle, the increasing acidity of the gastric content increasing the pylorospasm.

According to these observations, surgical therapy should be directed toward overcoming retention when it is responsible for increased acidity of the gastric contents. A large stoma to facilitate emptying of the stomach seems indicated. **Gastroduodenostomy** or **pyloroplasty** is preferable to gastrojejunostomy because of the greater resistance of the duodenum to digestion. In addition, the so-called ulcer gastritis is of the same acid origin as ulcer. Partial gastrectomy is not indicated because the development of typical ulcers in the wall of isolated stomachs proves that pure gastric juice can digest the gastric mucosa and makes it unnecessary to postulate a specific loss of resistance as the cause of gastric ulcers which should also respond to drainage and dilution of pure gastric juice.

**Diagnosis.**—Gastric ulcer is much more commonly benign than malignant, but there are no infallible signs, except the findings of microscopic investigation, which prove that a given lesion is benign. A. B. Rivers and T. J. Dry (Arch. Surg. 30:702 (Apr.) 1935) report case histories demonstrating that practically all signs and symptoms may at times fail to indicate the nature of a lesion, and give the reasons why the symptoms of benign and malignant ulcers may be identical.

Because of these facts it appears that unless contraindications to operation are present, it is usually safer to treat gastric ulcers surgically and to use nonsurgical methods of treatment only when it is possible to keep the patient under close observation for a prolonged period of time.

The significance of *erythrocytosis* in gastroduodenal ulcers is pointed out by

L. Ugelli (Policlinico (sez. chir.) 42: 544 (Sept. 15) 1935). The author examined the blood of 92 patients suffering from gastroduodenal ulcers, the presence of which was confirmed at the operation in all cases. The presence of erythrocytosis was proved in 74 per cent. of the patients suffering from duodenal ulcers, in 40 per cent. having gastric ulcers, and in 40 per cent. of a group of persons that had had gastric resections performed from 7 months to 3 years before the hematologic examination. In 2 patients presenting gastric disturbances associated with hyperchlorhydria there was no erythrocytosis. The author states that the presence of erythrocytosis is of value in the diagnosis of gastroduodenal ulcers. He discusses several hypotheses on the genesis of erythrocytosis and states that it does not originate in gastric hypersecretion. Both erythrocytosis and gastric hypersecretion are manifestations of the hypervagotonic constitution that is characteristic of ulcerous patients.

**Differential Diagnosis of Gastric Ulcer and Cancer.**—W. J. M. Scott (Ann. Surg. 102:586 (Oct.) 1935) reports in detail 10 cases of chronic gastric ulcer and presents roentgenograms to demonstrate the impossibility of differentiating between benign and malignant gastric lesions without histological study. The conclusion is reached that many of the lesions which clinically appear to be simple ulcers are eventually proved to be malignant. Balfour's report on 100 gastric lesions treated only by gastroenterostomy without excision, in which after 5 years or more there were only 6 incidents of death from gastric carcinoma, is explained by the method of choice which automatically included those lesions chiefly on the posterior wall of the stomach, the upper half of the lesser curvature, and the cardiac end of the stomach, where the incidence of

malignant lesions is particularly low. Lesions of the pyloric antrum and the greater curvature, where there is a greater likelihood of malignancy among questionable lesions, were excluded. Therefore by this process of selection an incidence of 6 per cent. of carcinoma is not surprising.

**Radical resection** is advised for all lesions which do not respond by improvement to a clinical test for malignancy in the chronic gastric ulcer. The criteria of improvement are: within the first week, diminution of symptomatology; within the second week, almost complete disappearance of symptoms plus absence of occult blood in the stools. The third week, the size of the ulcer niche should decrease at least by one-third and thereafter continuous decrease of the ulcer to disappearance, as determined by x-ray examination. Should at any time during the therapy there be a recurrence of symptoms or an increase in the size of the ulcer niche, surgical therapy becomes indicated.

In pointing out diagnostic errors in gastric ulcer and cancer, H. von Haberer (Deutsche Ztschr. f. Chir. 245:744 (Nov. 23) 1935) states that differential diagnosis between a callous ulcer and carcinoma of the stomach and duodenum is not always possible. The percentage of errors of this type has not been reduced in his material in spite of considerable advances in the clinical and x-ray studies and of the experience gained at the operating table. In the 3125 gastric resections performed by the author, 180 diagnostic errors of this type were committed. He feels that further reduction in the percentage of errors could be brought about by a reliable cancer test, which unfortunately does not exist at present. In his experience, malignant degeneration of an originally benign gastric or duodenal lesion occurred with sufficient frequency to

influence the surgeon's attitude toward the type of operative intervention. He reports a case in which a benign (ulcer) and a malignant lesion coexisted side by side in the same stomach and concludes that extensive resection in the presence of an ulcer is not only justified but imperative. It is to be regarded as a prophylaxis against carcinoma and, provided no vital contraindications exist, should always be preferred to the palliative operations for the exclusion of the ulcer.

**Treatment of Peptic Ulcer.**—According to A. Ochsner, M. Gage and K. Hosoi (Surg. Gynec. and Obst. 62: 257 (Feb.) 1936), the treatment of peptic ulceration has in too many instances been focused on the ulcer itself without realization that the ulcer is merely a symptom. The *causes* for peptic ulcer can be divided into 2 groups: one in which the factors are not amenable to therapy but are inherent and predisposing, and the other in which they are precipitating but can be corrected. The inherent or predisposing factors are tissue susceptibility and constitutional predisposition. The precipitating factors are hypersecretion, hyperacidity, focal infection and gastric trauma. Tissue susceptibility, which is an inherent quality present in all individuals, is the vulnerability of certain portions of the gastrointestinal tract to peptic digestion, such as the lesser curvature, pylorus, duodenal cap, jejunum and other portions of the intestinal tract subjected to the acid gastric chyme, as Meckel's diverticulum containing islands of gastric mucosa. Constitutional predisposition, although difficult to define, is unquestionably present in most if not all patients with chronic gastroduodenal ulceration.

As the predisposing factors are not amenable to therapy, the treatment of peptic ulcer consists in the prevention

and the correction of the precipitating factors. The peptic ulcer patient must abstain from activities that increase gastric secretion and acidity. In addition to this abstinence, neutralization of gastric acidity is favored by a **diet** consisting of frequent small feedings, as food is an important neutralizing agent. Administration of **mucin** is of value in controlling hyperacidity in many cases. Restoration of the normal function of the pyloric sphincter is of importance in the therapy of peptic ulcer, because it relieves gastric retention and also diminishes secretion, which is stimulated by gastric retention. The relaxation of the pyloric sphincter permits free regurgitation of the alkaline duodenal secretion into the stomach and favors neutralization. All **foci of infection** must be **removed**, because they can act either directly, by producing a specific inflammation in the stomach or duodenum, or reflexly, when within the abdomen, by producing pylorospasm. To minimize gastric trauma, only **bland foods** containing no roughage should be allowed. Because of the constitutional predisposition to ulceration, it is imperative that the patient change his mode of living. The surgical treatment of peptic ulcer consists largely in the treatment of complications, such as mechanical obstruction, perforation, repeated hemorrhages and danger of malignant change. In a case of pyloric occlusion with prolonged gastric retention and hypoacidity, **gastroenterostomy** is the procedure of choice. In cases with hyperacidity or normal acidity, because of the increased susceptibility of the jejunal mucosa to the acid gastric chyme, the **resection of the pyloric sphincter** or the performance of a **gastroduodenostomy** is to be preferred to gastrojejunostomy. The duodenal mucosa is more resistant to the acid gastric chyme than is the jejunal mucosa. The *chronic calloused ulcer*

in the stomach, which does not respond readily to therapy, should be operated on and **radical resection** done, because of the danger of malignant change.

The following *indications for surgery in duodenal ulcer* are given by J. A. Wolfer (Northwest Med. 35:5 (Jan.) 1936):

1. Those of recurrent or unyielding lesions which have failed to respond to medical therapy. This group should be divided into: (a) those with fairly normal acid curves and motility, and (b) those with high acid curves and hypermotility.

2. Cases with repeated hemorrhage.

3. Cases with obstruction.

4. Cases of a progressive nature in which, despite medical treatment, excessive pain, vomiting, and bleeding occur.

5. Cases with perforation.

The **surgical treatment** of duodenal ulcer must be adapted to the requirements of the individual case. In cases in which the ulcer is not adherent to the pancreas, conservative therapy is reasonably effective, whereas in the cases of emotional individuals with hyperacidity and hypermotility, gastroenterostomy is contraindicated because it is frequently followed by jejunal ulcer. For cases of the latter type a high **subtotal gastrectomy** such as the **Polya operation** is today regarded as the operation of choice.

Duodenal lesions with *repeated hemorrhage* often constitute a problem. In the cases of patients who have had several hemorrhages, operation should always be performed preferably in an interval between hemorrhages. The pathological findings vary. In some cases no open lesion can be found. As a rule, **subtotal gastrectomy** should be done.

The author also outlines cases of *gastric ulcer in which surgery is indicated*:

1. Those with perforation to the liver or pancreas.

2. Those of large or chronic ulcers in which malignancy is suspected.

3. Those of hourglass contraction.

4. Those of a progressive nature associated with excessive pain, vomiting, and bleeding.

5. Those with perforation.

6. Those with repeated hemorrhage.

As a general rule, gastric lesions are treated by **subtotal resection**. In cases in which the patient has been starved because of the ulcer symptoms and those in which the adequacy of the suture line is questionable, a **complementary jejunostomy** should be added to provide a means for immediate nourishment and to place the stomach at rest so that healing of the suture line may occur without danger of leakage.

The author discusses also the problems of *ulcer cancer*. According to his experience, the size of the lesion is of no great aid in determining its nature. Large spreading peptic ulcers of the stomach are encountered as frequently as small carcinomatous ulcers. The clinical history may be very misleading during the early stage of the disease. X-ray findings are also often misleading or of no value. However, there is little question that gastric symptoms appearing in an individual over 40 years of age who has had no previous complaints is very suggestive of cancer. Since it is impossible to differentiate gastric ulcer from gastric carcinoma with certainty or to determine whether an ulcer will become cancerous, the only hope for cure lies in **early resection**.

In conclusion, the author states that many poor, if not disastrous, results have been due to indiscriminate surgery or illogical operative procedures. Operations have been condemned because they have been performed when they

were contraindicated. This is true of gastroenterostomy.

For the best results in cases of peptic ulcer coöperation between the internist and surgeon is essential. If each case is individualized and is studied from the viewpoint that peptic ulcer is the local manifestation of a constitutional disease and if the disease is treated as a whole, fewer cases will reach the stage at which surgery is necessary. If the cases requiring surgery are further studied, it will be possible to find logical surgical procedures which will relieve the symptoms in a large number of them.

RESULTS OF SURGICAL TREATMENT IN GASTRIC AND DUODENAL ULCER.—The study of the experiences of the Metropolitan Life Insurance Company by L. I. Dublin (Proc. A. Life Insur. M. Dir. America, 1936) on cases with a history of peptic ulcer shows definitely that they are largely substandard. All surgical cases are, in fact, substandard and additional ratings are called for where there is a history of preoperative perforation or hemorrhage. A post-operative history of hemorrhage, perforation, or recurrent or marginal ulcers warrents rejection. On the other hand, a simultaneous appendectomy in surgical cases is not an unfavorable factor.

In regard to these surgical cases, the results, both of this and other insurance studies, must be construed as ordinarily applying much to duodenal ulcer. The reporting of the site of the ulcer in the general run of cases is so poor that insurance experience affords no adequate basis for judging the true rating for gastric ulcer. The large difference in mortality between duodenal and gastric ulcers in the published experiences of several clinics, despite their inadequacies, must in the meantime, guide the insurance company in the rating of such cases. Investigation of

the prognosis of gastric ulcer for insurance purposes is badly needed, and it is hoped that it may soon be done on the basis of a joint study by several companies of cases in which a full hospital report is available or on the basis of a follow-up study of one or more of the large surgical clinics.

In *surgical cases*, the insurance company may be somewhat more lenient where they know that the operation was performed by an especially qualified surgeon or was done in the best grade clinics. To aid them in gaining this information, the insurance company should try to obtain a statement from the surgeon. This should give them an estimate not only of his ability, but also of the credibility of the statement. Dublin feels they may then have reliable information on the site of the ulcer. Where the statement is not satisfactory or one cannot be obtained, the insurance company should be more cautious in its ratings. They must not forget, however, that the prognosis in surgical peptic ulcer is by no means entirely in the hands of the surgeon, but to a very large extent, is up to the patient.

Applicants with a history of *medical treatment* for peptic ulcer can, on the whole, be given lower ratings than the surgical cases, except those with a history of hemorrhage, which definitely calls for a high rating. In general, the cases that do not come to operation are, on the average, milder than cases which are operated. The insurance company must not lose sight of the fact, however, that their experience, as well as that of other insurance companies on medical ulcers, does not truly portray the prognosis, because these experiences contain a number of cases in which the original ailment was not ulcer. In order to be accurate, Dublin feels they need a careful diagnosis by an expert. The better cases can then be selected.

The chronic nature of peptic ulcer, of which there are many evidences in this study, means that the company cannot pay much attention in their ratings to the period elapsed between illness and application for insurance. Likewise, there is no real basis for differential ratings according to age. While it is true that the mortality from cancer of the stomach increased definitely with age, a surprisingly large number of cases have their onset of malignancy in the thirties. Moreover, the excess mortality from recurrent peptic ulcer overshadows that from gastric cancer.

So far as the Company's small experience on women with a history of peptic ulcer goes, no differential ratings according to sex are warranted.

Consideration should be given to the build of the applicant in rating a history of peptic ulcer. The fact that he has been able to gain or maintain his weight is a favorable sign, especially in the medically treated cases. Indeed, persons who are of normal weight or moderately overweight in this medical group can safely be taken with little extra rating a few years after their illness if there were no complications. In surgical cases, the difference in favor of the heavier builds is slight, but may be given consideration in borderline cases.

In regard to *cancer*, there is not much the company can do to protect itself. In some of the deaths from gastric cancer, especially where the period from illness to death was relatively short, it is entirely likely that the original illness was cancer of the stomach, although the original diagnosis was incorrect or unknown to the applicant. On the other hand, some of these applicants probably knew but concealed the facts when they applied for insurance.

In commenting on factors governing results of the surgical treatment of duodenal ulcer, D. C. Balfour (Ann.

Surg. 102:581 (Oct.) 1935) states that the best results, insofar as the relief of symptoms is concerned, are obtained for patients (particularly women) of middle age with impaired motor function, low acidity, and a long-standing history of distress. Less satisfactory results are obtained, regardless of operation, the farther conditions are in opposition to the factors above mentioned, but this particular series of cases gives surprisingly little emphasis to this point. In respect to the value of the different types of operations, this study showed conclusively that if results are computed over a sufficient length of time after operation and surgical management has been well applied according to the circumstances in each case, the conservative operations present so many advantages that they are the operations of choice for chronic duodenal ulcer, both with and without complications. In particular, the value of **gastroenterostomy** clearly is apparent, for not only does it usually bring about complete and permanent healing of duodenal ulcer, but in the event of recurrence of ulceration in the stomach or jejunum, it is the only operation which permits restoration of normal continuity of the stomach and duodenum, an advantage which it is unnecessary to emphasize.

The *late results of surgical treatment* in 846 cases of benign lesions of the stomach and duodenum and of 432 operations performed for malignant disease of the stomach are given by E. Harms (Arch. f. klin. Chir. 185:241 (June 3) 1936). *Radical operations* for gastroduodenal ulcer gave entirely satisfactory results in 80 per cent. of the cases, while the indirect methods (*palliative operations*) gave good results in only 50 per cent. No difference was noted in the late results of the first Billroth and the second *Billroth operations*. Failure after *gastroenterostomy*

and pyloric exclusion were noted with the greatest frequency in the younger patients. It was only after the fifth decade that better results were noted. Even the penetrating duodenal ulcers not amenable to *resection* still offered a relatively good prognosis in persons past 50 years of age. Resection of the pylorus and antrum and segmental transverse resection are likewise followed by better results in the older patients. The first Billroth operation appeared to be best suited for the younger patients. The longer the lapse of time since the operation, the better were the results with the first Billroth operation, and the worse with the indirect procedures. Better late results could be expected when the resection of the pylorus and antrum was undertaken for an extensive ulcerative lesion than when it was performed for a superficial ulcer. Peptic jejunal ulcer was the principal cause of failure after *gastroenterostomies* and *pyloric exclusions* (13.4 and 15 per cent., respectively). The transverse resection gave an incidence of 7.8 per cent. of recurring ulcer and 6.1 per cent. of disturbances of motility. Following the second Billroth method of resection, the incidence of peptic jejunal ulcer was 0.8 per cent. and that of recurring ulcer 2.5 per cent. The failure to obtain good results after the first Billroth method of resection was because of recurring ulcer in 4.1 per cent. and narrowing of the anastomosis in 3.4 per cent. Of the 432 cases admitted with the diagnosis of *cancer of the stomach*, 75 per cent. were inoperable. The operative mortality was 32.9 per cent. Peritonitis was the most frequent cause of death. Most of the patients surviving the operation died within the first 2 years; 33 $\frac{1}{3}$  per cent. survived the 5-year period, and 8.3 the 10-year period. The best prognosis was offered by adenocarcinomas limited to the stomach with an average

duration of not more than 7 $\frac{1}{2}$  months. Prognosis appeared to be somewhat better in the older patients.

**ULCER OF PYLORIC SPHINCTER.**—In 11 years, J. S. Horsley (*Ann. Surg.* 103:738 (May) 1936) operated on 12 patients with peptic ulcer, either solely (9) or partly within the pyloric ring. A **partial gastrectomy**, a modification of the first method of Billroth, was done. That partial gastrectomy is the proper treatment for this type of ulcer seems to be supported by a consideration of the clinical and pathologic features of the lesion. A true ulcer of the pyloric sphincter always has a background of pyloric (gastric) mucosa, because this mucosa normally lines the pyloric sphincter. An ulcer of the pyloric ring, then, is a gastric ulcer, the symptoms of which are usually accentuated. The average age of these patients was 46.6 years. Two of them were women and 10 were men. The average duration of symptoms was 10 $\frac{3}{4}$  years, the duration of the symptoms varying from 3 months to 20 years. Several of the patients gave a longstanding history of indigestion, but the severe symptoms were of only recent date. There was severe pain in 9 cases, mild pain in 1 case, and 2 patients complained of no actual pain. In the latter 2 cases there was vomiting of much blood, and some bleeding in another case. In 9 cases there was a history of vomiting. A gastric analysis was done in 10 of these cases. The average value for free hydrochloric acid was 32.9 units. The highest average value of free hydrochloric acid in any one case was 75. In 2 cases there was no free hydrochloric acid. In 10 cases an x-ray examination was made, and in 3 obstruction was present after 24 hours.

**BLEEDING ULCER.**—The article of F. Umber (*Deutsche med. Wchnschr.* 61:1265 (Aug. 9) 1935) reports on 433

medically treated cases of severe hemorrhage from ulcer which were among 1852 cases of gastric and duodenal ulcer seen in the past 16 years. Forty-one (9.5 per cent. of the patients with hemorrhage and 2.2 per cent. of the total number of patients with ulcer) died of hemorrhage. Therefore the mortality of massive hemorrhages due to ulcer which are treated medically is higher than is generally assumed. In 21 of the 41 patients who died, an open eroded artery was found to be the source of the bleeding.

The *diagnosis of the source* of the bleeding must be based on the history and the symptoms. The *clinical diagnosis* can be made only after the hemorrhage has completely ceased. Of most importance is arrest of the hemorrhage. The absolute amount of blood lost is of less significance than the tendency of the bleeding to continue or recur. The hemoglobin and pulse curves are indicative of the patient's condition. When the hemoglobin is less than 50 per cent., there is danger, and when it is between 20 and 30 per cent., the condition is critical. As a rule, the pulse rate increases.

At first, the patient should be kept **absolutely quiet in bed** and given **pantopon** or some other narcotic. To arrest the hemorrhage, from 10 to 20 c.c. (2½ to 5 drams) of a **hypertonic solution** with a 10 per cent. content of **sodium chloride** and a 0.02 per cent. content of **calcium chlorate** or a 10 per cent. content of **calcium gluconate**, and, in addition, 0.2 c.c. (3 minims) of a solution of **stryphnon** per kilogram (2½ pounds) of body weight may be given by intravenous injection several times daily. When the **stomach** becomes filled with coagulated blood, it is **washed out with ice-water containing adrenalin**. The emptied stomach contracts under the stimulation of the cold. On the first day nothing should

be given by mouth. Thirst may be prevented by the subcutaneous, intravenous, or rectal administration of **normal salt solution containing sympatol**. On the second day, **cracked ice**, **cold gelatin**, **milk gruel**, and a 5 per cent. **dextrose solution** may be given in teaspoonful quantities. Small amounts of **chilled butter** are of value to supply calories and decrease the secretion of hydrochloric acid. Soon, the patient's strength may be increased more quickly by the frequent administration of small quantities of fluids and gruels richer in calories and protein. The **diet** should not contain meat or meat extractives. The vitamin requirements may be met by 2 intravenous injections of 1 c.c. (16 minims) of **cebione**. Nutritive enemas are to be avoided, as they stimulate gastric peristalsis and secretion. In some cases **blood transfusion**, to replace the blood lost and stop the hemorrhage, may prove life-saving. The transfusion of from 300 to 500 c.c. may be repeated on several days. To stimulate the regeneration of blood after control of the hemorrhage, intramuscular injections of 2 c.c. (½ dram) of strong **pernæmyl** may be given daily on from 3 to 7 successive days, and then in doses of 4 c.c. (1 dram) once a month with the periodic administration of 1 Gm. (15 grains) of reduced iron.

Of the 39 patients with bleeding ulcer who were operated upon, only 32 could be traced. Twenty-five were cured—19 by **resection** and 6 by **gastroenterostomy**. Seven died in spite of the operation. Three of these had a gastric carcinoma. Therefore among the 433 cases of massive gastric hemorrhage there were 3 of gastric carcinoma which were not recognized before operation. Of the 29 other cases of bleeding ulcer coming to operation, 23 were cases of duodenal ulcer. In one case the source of the hemorrhage could not be determined.



The author concludes that massive hemorrhage from ulcer should first be treated medically, as in 82 per cent. of the reviewed cases the bleeding was controlled by such treatment. **Operation** is to be considered only when, despite medical treatment, the bleeding recurs, the hemoglobin and the patient's strength decrease, and the pulse rate increases. In cases of definite recurrent hemorrhage, operation should be performed, if possible, in an interval between the hemorrhages.

In the experience of J. J. Westermann (*Ann. Surg.* 101:1377 (June) 1935), 12 per cent. of gastroduodenal ulcers have been complicated by hemorrhage. In 75 per cent. of these cases the hemorrhage has been massive and recurrent. In every case **transfusion** had been given at least once, and frequently more often, either during the course of a medical regimen or as a preoperative or postoperative measure. These records show that transfusion has been completely ineffectual as a means of stopping hemorrhage. The advisability of operation during the hemorrhage is debatable. However, hemorrhage of such proportions elsewhere in the body is always treated as a surgical emergency. Patients operated on under these circumstances have survived. One immediate death occurred in a case complicated by carcinoma of the pancreas. In each instance in which the operation performed was of the indirect type, the hemorrhage continued. Westermann is of the opinion that **immediate surgery** of the direct type is justifiable in a large percentage of these cases and will prove permanently successful. The presence of the lesion can be determined only by careful inspection at operation with the duodenum open. **Preoperative and postoperative transfusions** are an absolute requirement of this procedure. Ten patients in this series died in the

hospital from continued hemorrhage while receiving most rigid medical treatment and, in many instances, daily transfusions. The source of massive hemorrhage that complicates gastroduodenal ulcer is from the posterior surface of the duodenum in a large majority of cases. The blood supply of this area makes gross hemorrhage possible without deep penetration of the wall. Exploration of the open duodenum is necessary to determine this source in all cases except those in which there are large penetrating ulcers of the crater type. Preoperative diagnosis is usually definite in these cases, but diagnosis of the posterior surface ulcer is extremely difficult and cannot be accurate.

#### **PERFORATION OF ULCER.—**

The experiences of H. J. Lang (*Beitr. z. klin. Chir.* 162:143, 1935) in the treatment of 152 cases of perforated gastric and duodenal ulcer, show that there was an unexplainable increase in the incidence of perforation in the patients with ulcer who were admitted to the hospital. Half of the patients with perforation were laborers of the type usually found in large cities. Many were chronic alcoholics. The majority were undernourished and weak because of protracted gastric disturbances and inability to follow difficult dietary regimes because of occupational or home conditions.

Twenty-two (14.5 per cent.) of the patients were women. Seventeen (77.3 per cent.) of the women died. Twelve of the women were not operated upon, being moribund when admitted to the hospital. The average age of the women was 63 years, a fact suggesting that in the differential diagnosis of doubtful abdominal conditions in women of advanced age, the possibility of perforated peptic ulcer should be borne in mind.

Most of the perforations occurred during the winter. No familial predisposition could be established. The

incidence was highest in chauffeurs and waiters. Smokers were well represented.

A significant observation was increased severity of the gastric distress, which may be interpreted as suggesting imminent perforation. This so-called augmented premonitory pain occurred in 50, or approximately one-third, of the cases. Vomiting, an increased pulse rate, and the temperature were of no value in the differential diagnosis.

Forty-five per cent. of the patients were operated upon within 6 hours after the perforation; 20.2 per cent., between 6 and 12 hours; 9.2 per cent., between 12 and 18 hours; and the remainder after 18 hours. Early operation was, therefore, possible in fewer than half of the cases. Board-like rigidity of the abdominal wall was always present. The differentiation from perforated appendix was very difficult. In advanced cases complicated by diffuse peritonitis it was practically impossible. The pain referred to the shoulder which was described by Oehlecker was of some value. Pneumoperitoneum is pathognomonic of ulcer perforation, but was not always demonstrable. The gastric crisis of tabes simulates ulcer perforation very closely, but a leukocytosis with a shift to the left suggestive of perforation is not found in the undifferentiated blood picture of gastric tabes.

It is often very difficult to find the site of the perforation. Occasionally there are multiple perforations. A second perforation was overlooked in 5 of the cases reviewed. There were 15 pre-cardial ulcers, 112 ulcers in the pyloric region, and 10 ulcers in the horizontal part of the duodenum. All of the lesions except one were on the anterior wall. The one exception was not found during operation, probably because the patient's poor condition, due to a perforation which had occurred 96 hours previously, did not permit extensive manipulation.

**Treatment.** — According to Lang (*Ibid.*), the most effective treatment was **simple closure**. This was always done with 2 rows of sutures. The first row consisted of interrupted catgut sutures going through all 3 layers. The second was of silk and included only the serosa and muscularis. The sutures should be inserted parallel with the long axis of the stomach so that, when the suturing is completed, the row will be at right angles to the long axis of the stomach. In the cases reviewed, **gastroenterostomy** was done only when stenosis appeared inevitable. The Newman (Braun) omental cuff **drainage** was used only in the most desperate cases. In a high percentage of the cases conservative treatment yielded satisfactory end-results and primary resection was avoided.

A. S. Brinkley (Virginia M. Monthly 62: 366 (Oct.) 1935) employed **simple closure** of the perforation and **jejunostomy** with **drainage** of the cul-de-sac in his last 5 cases of acute perforated duodenal ulcer, in which operation was performed during the last 17 months. There was 1 death. The *postoperative treatment* consists in **elevating the head of the bed** 12 inches; 500 c.c. of a 5 per cent. solution of **dextrose** is immediately given intravenously and by the flush method as proctoclysis, and **gastric lavage** with a warm solution of **sodium bicarbonate** is given with the **duodenal tube** from every 4 to 6 hours for the first 24 hours and continued if necessary. Every 4 hours 1 c.c. of **digifoline** or **digitalone** is given hypodermically, and  $\frac{1}{8}$  grain (0.022 Gm.) of a mixture of **opium** and **alkaloids** every 4 to 6 hours, if required. *Fluids are withheld by mouth.* **Feedings** every 2 hours are started **through the jejunostomy tube** at once. For the first 2 or 3 days 2 ounces (60 Gm.) of predigested beef in 2 ounces (60 c.c.) of warm water is given at one feeding,

and 4 ounces (120 c.c.) of peptonized milk at the next feeding. After this period a more liberal diet is allowed. Water is given between feedings. The drainage tube is removed on the third to the fifth day. Water is allowed by mouth in small quantities on the fifth day, liquids on the eighth to the tenth day. The catheter and sutures are removed on the tenth to the twelfth day and an ulcer diet is started on the fourteenth day. The patient is usually allowed to sit up in bed at the beginning of the third week and is discharged from the hospital during the third or fourth week.

**RESULTS.**—The results of 151 operations for perforation of gastric and duodenal ulceration are analyzed by G. Häussler (*Chirurg.* 8:206 (Mar. 15) 1936). There were 6 women in the group (4 per cent.). Operation was performed in 70 per cent. of the cases within the first 6 hours after the onset of symptoms and in 16.5 per cent. within the first 12 hours. The total mortality rate was 26.5 per cent. The mortality rate in the group in which operation was performed within the first 6 hours was 15.4 per cent., and that of the first 12 hours, 17.6; in the group in which operation was performed after 12 hours it was 69 per cent. A follow-up study was made in 86 cases and an x-ray study in 73. In 29 of the patients there developed an incisional hernia and in 13 a mild diastasis of the rectus muscle. The mortality in a group of 28 patients in whom suture of the ulcer alone was practiced amounted to 17.1 per cent. In a group of 83 patients in whom **suture of the perforation** and a **gastroenterostomy** was practiced, the mortality amounted to 18.1 per cent., and in a group of 22 having **partial resections** the mortality was 22.7 per cent. Only one-fifth of the patients in whom a gastroenterostomy was performed were free from complaints. In 8 there de-

veloped a peptic jejunal ulcer. Of these, 1 died of a profuse hemorrhage and the remaining 7 were submitted to the operation of partial gastric resection. In the group in which suture of the perforation was performed, half the number were free from symptoms. Pyloric stenosis occurred in 5 cases. The results in the group in which partial gastric resection was practiced were better; more than half of these were symptom-free and the remaining complained of mild symptoms on ingestion of a heavy meal. The patients who were not working were more likely to have complaints than those who returned to work. The authors have abandoned in the late years the addition of gastroenterostomy because of the poor results. They consider **simple suture of the perforation** the operation of choice and reserve the later operation of partial gastric resection for cases exhibiting more serious complications or symptoms.

#### **GASTROJEJUNAL ULCER.**—

In a paper dealing with gastrojejunal ulcer and gastrojejunal fistula, F. H. Lahey and N. W. Swinton (*Surg. Gynec. and Obst.* 61:599 (Nov.) 1935) state that in the years 1928 to July, 1934, there have been 1098 cases of gastrojejunal ulcer reported in the literature.

The authors note that gastrojejunal ulcer is now considered a serious and not unlikely complication of any operative procedure for ulcer in which the stomach is anastomosed to the intestine, and not a sequela peculiar only to gastroenterostomy.

**Symptoms.**—The time of onset of symptoms of gastrojejunal ulcers varies from a few weeks to many years, up to 21 years (Lublin). In 50 cases taken at random, 50 per cent. of the recurrences (gastrojejunal) occurred within 2 years following operation.

In general, it may be said that the longer period patients who have had

anastomoses of the jejunum to the stomach go without recurrence of ulcer symptoms, the less likelihood is there of the occurrence of gastrojejunal or jejunal ulcer. It must be assumed, in spite of this, however, that in any patient who has had the jejunum anastomosed to the

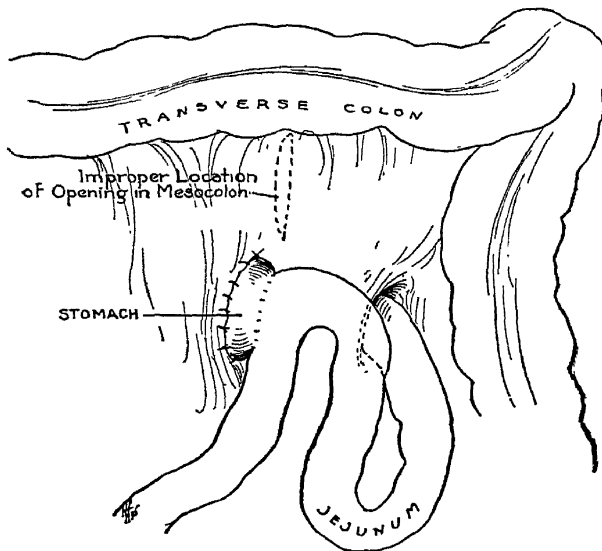


Fig. 9.—Illustration showing diagrammatically the proper and improper location of the opening in the gastrocolic omentum for a gastroenterostomy. It can be appreciated when the opening is made as shown in dotted lines close to the transverse colon, that should a gastrojejunal ulcer occur, it almost must involve the transverse colon in the surrounding exudate and so penetrate frequently into the colon and produce a gastrojejuno-colic fistula. This drawing illustrates a jejunal loop of sufficient length to permit easy resection and anastomosis should a jejunal ulcer occur as opposed to the no-loop type of jejunal anastomosis. (Lahey and Swinton: Surg., Gynec. and Obst.)

stomach, the development of a gastrojejunal ulcer is always possible, regardless of the time factor.

There are certain features of the symptomatology of gastrojejunal ulcer which are characteristic of this condition. In patients who have developed post-operative gastrojejunal ulcer, there is usually a period after the performance of the gastroenterostomy in which the patient is entirely relieved of the ulcer symptoms for which the operation was done, with a later return of ulcer symptoms not infrequently of greater in-

tensity than before the operation. The *ulcer pain* is less satisfactorily relieved by food and alkalines than was the pain associated with the original ulcer. The pain is less consistently related to meals than was the original ulcer pain. The distress associated with the occurrence of gastrojejunal ulcer is less tractable to all methods of treatment than was the distress associated with the original ulcer.

*Hemorrhage and melena* are, the authors believe, somewhat more frequently associated with marginal ulcer than with the duodenal and gastric ulcer.

The point of *abdominal tenderness* in duodenal ulcer (and duodenal ulcers make up the great majority of ulcers, 10 duodenal to 1 gastric ulcer in the authors' experience) is usually in the right upper quadrant, while in gastrojejunal ulcer the point of abdominal tenderness tends to be lower down, a little above and to the left of the umbilicus. This is the point on the abdominal wall opposite which the anastomosis of the jejunum to the stomach commonly rests and with gastrojejunal ulcer it is usually tender over the stoma here.

Symptoms of *ulcer perforation* in any patient who has had a gastroenterostomy performed, particularly for duodenal ulcer, should make one suspect the possible presence of a perforated gastrojejunal ulcer.

**Diagnosis.**—The recurrence of symptoms suggestive of ulcer after operative measures for ulcer, particularly duodenal ulcer, should always suggest the probability of gastrojejunal ulcer. The presence of tenderness over the stoma on fluoroscopic visualization of the stoma likewise suggests it. The presence of a fleck at the stoma after the ingestion of a small amount of barium suggests that this is due to a small amount of bismuth remaining adherent to the ulcer. The presence of a gastrojejuno-colic fistula

demonstrable by x-ray definitely settles the diagnosis of gastrojejunal ulcer.

The closure of the stoma likewise suggests the presence of a gastrojejunal ulcer, as does persistent deformity of the stomach, stoma or jejunum.

**Treatment.**—There is a distinct conviction on the part of most individuals dealing with ulcer that patients with gastrojejunal ulcers seldom respond satisfactorily and permanently to medical treatment, but in all cases medical treatment should be carried out to reduce acidity, thus perhaps lessening the area of acute reaction about the ulcer and improving the general condition of the patient as an operative risk. In addition, a number of patients with undoubted gastrojejunal ulcer have been observed who have been able to get along satisfactorily for a number of years on medical treatment.

Since any patient who has developed a gastrojejunal ulcer has demonstrated that he falls in the group of patients who are particularly liable to recurrent ulcer, it is the feeling of many surgeons and it is the authors' conviction that any surgical measure short of radical **subtotal gastrectomy** will probably be followed by a recurrent ulcer and, as shown in figures from the literature, even with radical partial gastrectomy, recurrent gastrojejunal ulcer will still occur in a small percentage of cases. In defense of this position it must be admitted that the best operative procedure for such recurrent ulcers is the one which is followed by the most complete postoperative anacidity and that operation is undoubtedly subtotal gastrectomy. The mortality, however, in such an extensive operation as is necessary with gastrojejunal ulcers and on patients frequently in poor condition, is considerable, being reported by one of its ardent advocates as 20 per cent. and the authors' mortality rate has been 15

per cent. On the other hand, it is claimed by many that the unhooking of the gastroenterostomy and restoration of the digestive stream is frequently followed by a recurrence of the original ulcer and such has been the authors' experience—40 per cent. recurrent duodenal ulcer in such procedures.

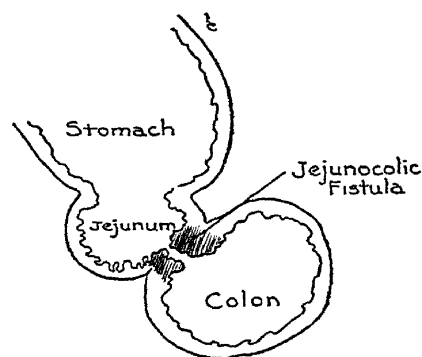


Fig. 10.—Drawing indicating diagrammatically how the colon becomes adherent to the jejunum and the ulceration breaks into it. (Lahey and Swinton: Surg., Gynec. and Obst.)

There are certain basic facts which must be admitted in any discussion of the surgical treatment of peptic ulcer. It must be admitted that both physicians and patients have accepted and do accept the original peptic ulcer with all too great complacency. The mortality from *hemorrhage* alone in this group of patients while in the authors' hands in the hospital has been 5 per cent., 1 in every 20 patients. It must be admitted that **gastroenterostomy** is not a desirable type of operative procedure to be routinely applied to the surgical treatment of peptic ulcer as it has been in past years. It must be admitted that **pyloroplasty** (the safest of all operations for ulcer) is difficult to apply in many of the patients with duodenal ulcer, due to the scarring and distortion of the duodenum by the ulcer. It must be admitted that **radical partial gastrectomy** gives the highest percentages of complete and permanent relief from ulcer symptoms and the lowest per-

centage of recurrent anastomatic ulcers, but it must also be frankly admitted that it has and probably always will have a mortality rate, except in selected cases which both to the patient and surgeon is disturbing.

It must be admitted that while small gastrojejunocolic *fistulas* can be handled

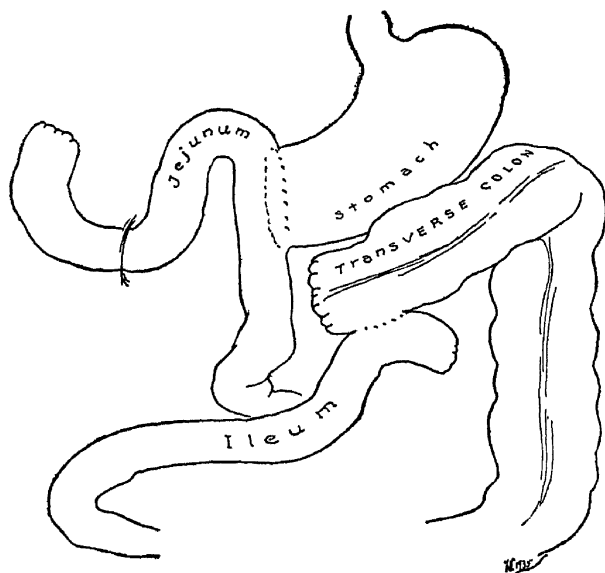


Fig. 11.—Drawing diagrammatically illustrating the ideal procedure for gastrojejunocolic fistula: Resection of stomach including old gastroenterostomy and gastrojejunal ulcer, resection of portion of jejunum containing ulcer, end-to-end anastomosis of jejunum, resection of ascending colon, hepatic flexure, and a portion of transverse colon beyond the fistula into it, anastomosis of jejunum to cut end of stomach and anastomosis of ileum to transverse colon. This, unfortunately, is too much surgery for many of the patients with gastrojejunocolic fistulas to endure. Up to the present it is, however, the only plan whereby large gastrojejunocolic fistulas may be removed without contamination of the peritoneum by colon contents. It must be understood that this discussion does not include the small gastrojejunocolic fistulas which can usually be handled quite satisfactorily by separation and inversion. Lahey and Swinton: Surg., Gynec. and Obst.)

by operative procedures with reasonable satisfaction, a situation must be faced which, at least in the authors' hands, has up to the present proved almost insurmountable, when the fistulous opening into the transverse colon in gastrojejunocolic fistula is a large one, for example,

the size of a quarter, half-dollar or dollar, as it so often is.

In operating upon such large fistulas between the colon, stomach, and jejunum, the surgeon is faced with the dilemma of producing peritoneal contamination with colonic contents on separating the large fistula, with the need of trying to close a fistulous opening into the colon when that structure is badly indurated and so holds stitches badly, or with the necessity of doing a block removal of stomach, jejunum, and mid-colon, which necessitates 3 resections at one sitting, resection of the stomach, jejunum, and transverse colon (Fig. 11). The authors have successfully accomplished this, but it is a procedure of too great magnitude to be routinely applicable to this condition with a reasonable mortality. They have employed numerous procedures in an attempt to decrease the danger and mortality in these trying cases. Twice they have cut the stomach across proximal to the old anastomosis and so proximal to the gastrojejunocolic fistula, have closed the distal end and anastomosed a segment of jejunum by the Polya method distal to the fistulous connection between the stomach, jejunum and colon. Lahey and Swinton have hoped by this procedure to cause the ingested food to pass directly into the jejunum beyond the old gastrojejunostomy and beyond the fistulous opening into the colon (Fig. 12), thus segregating the section of the stomach and jejunum containing the ulcer and also segregating the fistula. By this plan it was hoped that food would be absorbed and utilized as it passed along the jejunum and not through the fistulous opening into the transverse colon, resulting as it has in some of the cases in a weight loss of several pounds a week.

Both patients made excellent operative recoveries but one died a cardiac death 26 days after operation when ready to

go home and the other died of intestinal obstruction 6 months after leaving the hospital. The authors admit that when they are faced with a patient with gastrojejunal ulcer which has perforated into the transverse colon, and produced a gastrojejunocolic fistula of large caliber and surrounded, as they always are, by a large area of induration, they are still considerably at a loss as to how it can

aspect of the ulcer situation, but nevertheless feels it his duty again to repeat that unless patients with a peptic ulcer are frankly told of this list of admissions and are not permitted to assume that the operation which they accept is an entirely satisfactory one, then how can they ever be made to take their responsibility seriously or finally as they all eventually must?

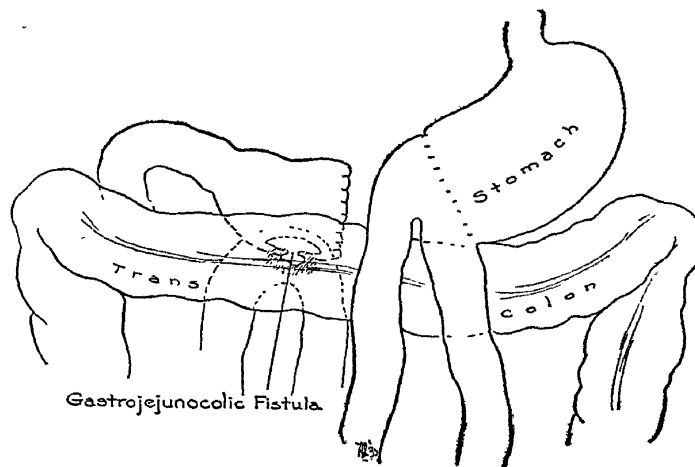


Fig. 12.—Drawing illustrating procedure employed twice by writer. Through a left rectus incision, the stomach is cut off proximal to ulcerated stoma and fistula and jejunum beyond gastroenterostomy anastomosed to cut end of stomach. In both cases operations were immediately successful but ultimately (26 days and 3 months) the patients died of conditions, one coronary disease and one untreated intestinal obstruction, not directly related to the procedure. This plan may still prove a useful procedure in dividing the radical removal of stomach, colon, and jejunum in the large gastrojejunocolic fistulas into a less shocking two-stage procedure. It was hoped that by sidetracking gastric contents by this procedure, closure of the ulcer and lessening of the induration about the fistula might occur. Autopsy in both of these cases, in one 26 days and the other 3 months after after operation, showed induration to be still marked and ulcers unhealed. Should this procedure again be employed, the authors believe they would remove the lower end of the stomach, jejunum and right colon through a right rectus incision at the end of 3 weeks. (Lahey and Swinton: Surg., Gynec. and Obst.)

be surgically cared for with reasonable safety.

Lahey and Swinton admit, finally and most importantly, that most patients are not aware of how unsatisfactory the situation is as relates to the surgery of peptic ulcer and so do not feel as strongly as they should about the compelling need for modification of living, eating, smoking, and drinking habits, in order that they may avoid the necessity of facing an unsatisfactory surgical procedure or a satisfactory one with an unsatisfactory risk rate. Lahey is self-conscious of having harped upon this

E. S. Judd and M. T. Hoerner (Ann. Surg. 102: 1003 (Dec.) 1935) state that when jejunal ulcer is known to exist, any one who persists in treating the lesion by medical management for a prolonged period assumes a great responsibility in view of the complications that may develop. The results of treatment of the 597 patients comprising the authors' study illustrate the value of surgical measures in cases of jejunal ulcer, for secondary procedures were required in only 6 per cent. of the traced cases. The development of a jejunal ulcer suggests that the patient probably will not

show a greater degree of toleration to another anastomosis between the stomach and the jejunum; therefore, a radical change in the gastrointestinal relationship is indicated and, when this is established, it must maintain the normal continuity as nearly as possible. The **first operation of Billroth** offers the ideal solution to the problem. It may be difficult to perform in some cases in

which a considerable portion of the stomach has been removed at the primary operation; however, if the procedure can be employed, the continuity of the gastrointestinal tract will be established in a better way than it would be by a Polya operation. The incidence of jejunal ulcer following gastrojejunostomy for duodenal ulcer is about 2.8 per cent.

## ANESTHESIA

By HENRY S. RUTH, M.D.

**Postoperative Respiratory Complications.**—An excellent review of this important type of postoperative complication was published by E. A. Rovenstine and I. B. Taylor (Am. J. M. Sci. 191:807 (June) 1936). They state that "Too often such reports have not been substantiated by accurate, carefully collected statistics. They may merely represent the author's impression or may consider one single factor, namely, the agent. It has been a firm conviction in this clinic that other factors such as the ability of the surgeon and anesthetist, the anesthetic technic, the time required for operation, the depth of narcosis and many other circumstances should be taken into account in evaluating postoperative morbidity and mortality. It was to correlate the majority of the factors common to surgical procedures and learn their influence on postoperative pulmonary complications that the present study was undertaken.

"It is readily agreed that statistics are not infallible but if they are carefully recorded and tabulated they offer a worthy substitute for vague conclusions which cannot be verified by records. The statistics in this report were compiled from the records completed during the calendar years 1933-1934. They

represent the first two years' experience with an improved anesthetic record system at the Wisconsin General Hospital."

The anesthetic agents employed were ether, nitrous oxide ( $N_2O$ ), ethylene ( $C_2H_4$ ), tribromethanol, procaine and cyclopropane ( $C_3H_6$ ). Drugs such as chloroform, barbituric acid derivatives and other drugs, employed in less than 100 cases were excluded. All anesthetics were administered by members of the anesthetic staff of the Wisconsin General Hospital. Premedication, with regard to agents employed for this purpose, varied little; the usual drugs being morphine and scopolamine for the inhalation types of anesthesia, and a derivative of the barbituric acid series when procaine was to be administered. All complications were reported. The complications which occurred were as are shown in the table on page 401.

"Marked seasonal variation is contingent upon the prevalence of respiratory diseases in the population outside the hospital. The presence of any respiratory tract infection, even mild pharyngitis, substantially increased the incidence of postoperative respiratory infections." Whereas there was an incidence of postoperative respiratory complications for all cases of 6 per cent., this was increased as follows by the



presence of certain preoperative infections:

|                   |      |
|-------------------|------|
| Pharyngitis ..... | 10%  |
| Oral sepsis ..... | 12-% |
| Emphysema .....   | 15+% |
| Cough .....       | 25%  |

It appears that if the agents are selected with discrimination, the influence of the agent may not be great, for it was shown that *no* complications occurred with the various agents as follows:

|                      |       |
|----------------------|-------|
| Nitrous oxide .....  | 94.50 |
| Ethylene .....       | 86.10 |
| Ether .....          | 92.20 |
| Cyclopropane .....   | 93.50 |
| Procaine .....       | 92.00 |
| Tribromethanol ..... | 94.30 |

These figures were, however, further influenced by the fact that nitrous oxide was employed for obstetrical analgesia, in dental extractions and for many superficial operations, while tribromethanol was used almost exclusively in good risk patients for ocular surgery.

The type of preoperative physical risk greatly influenced the incidence of respiratory complications, for the more serious the risk, the greater the incidence. The depth of narcosis exerted a substantial effect, which emphasizes the fact well-known among anesthetists that deeper than first plane, third-stage anesthesia should not be instituted and maintained unless necessitated by the surgical procedure and the demands of the surgeons. It is interesting to again have verified that with spinal anesthesia, high anesthesia caused almost  $2\frac{1}{2}$  times as great an occurrence as with low spinal, when the classification between the two was based on the presence or absence of interference with intercostal activity.

"The most striking influence upon postoperative respiratory complications was shown by the duration of opera-

#### RESPIRATORY COMPLICATIONS IN 7874 ANESTHESIAS

| Complications                   | No. | Per-centage of All Cases |
|---------------------------------|-----|--------------------------|
| Pneumonia, lobar and bronchial  | 49  | 0.60                     |
| Pneumonia, hypostatic. ....     | 8   | 0.10                     |
| Pneumonia, tuberculosis. ....   | 2   | 0.02                     |
| Collapse, partial. ....         | 22  | 0.30                     |
| Collapse, massive. ....         | 13  | 0.20                     |
| Bronchitis. ....                | 22  | 0.30                     |
| Laryngitis. ....                | 144 | 1.80                     |
| Cough, slight. ....             | 287 | 3.60                     |
| Cough, severe. ....             | 89  | 1.10                     |
| Hiccough. ....                  | 35  | 0.40                     |
| Obstruction, upper respiratory. | 32  | 0.40                     |
| Rhinitis. ....                  | 27  | 0.30                     |
| Pleurisy. ....                  | 11  | 0.10                     |
| Sore throat*. ....              | 33  | 0.40                     |
| Miscellaneous. ....             | 24  | 0.30                     |
| All respiratory complications.  | ... | 6.00                     |

\*Endotracheal anesthesia only.

tion. Whereas operations lasting 1 hour or less have a morbidity incidence less than the average for the group, the ratio for procedures requiring a longer time increases markedly. When the duration was 1 to  $1\frac{1}{2}$  hours, the respiratory complications doubled those of 1 hour. When 2 hours were needed, the percentage of complications was more than 3 times that of 1 hour. In procedures lasting 3 hours, more than 31 per cent. of the patients had some respiratory complication. The group requiring more than 4 hours had the highest incidence of respiratory complication. Despite the seriousness of the longer surgical manipulations and the grave risks encountered in the majority of them, duration of operation alone appears to be a definite factor influencing respiratory morbidity.

"That the ability, training, and experience of the anesthetist modifies morbidity is well shown in these statistics. Teaching students and training anesthetists will be accomplished by an increase in postoperative complications."

## DRUGS AND METHODS.—

**AVERTIN.**—A valuable use for tribromethanol is emphasized by S. Lessinger (Proceedings of Meeting of Am. Soc. Anesthesia (Feb. 13) 1936) for *encephalography*, with a suggested technic which was employed for 61 anesthetics. He calls attention to the discomfort usually caused the patient by this procedure, if not anesthetized, and also that the drugs commonly employed in clinical anesthesia may produce physiological disturbances detrimental to successful results and so constitute too great an additional hazard to the patient.

He suggests that tribromethanol may be employed as a technic of anesthesia which may assist in making *encephalography* a procedure without discomfort or increased danger to the patient, without inconvenience to the operator, and with the goal of successful completion of the procedure. He states that the drug has enjoyed an extensive application for manipulations involving the central nervous system, since it will produce some degree of narcosis for several hours; it is very convenient to use and requires a minimum of apparatus; and more particularly because it has not been shown to increase intracranial pressure.

The technic suggested is as follows:

Preliminary preparation begins with a thorough soap suds enema given at least 5 to 6 hours before operation. This is followed by a saline enema until clear. The importance of this thorough cleansing cannot be over emphasized, if sufficient anesthesia for *encephalography* is to be obtained. Further preparation consists of a restriction of both fluids and food for several hours. Premedication is obtained with barbiturates.

Tribromethanol is given in doses not to exceed 100 mg. per kilogram of body weight. In about one-half of the author's cases a full dose was given at once. In the other half the fractional method of administration was used. In this method a 2½ per cent. solution of the drug in distilled water is prepared at a temperature of 40° C., the solution containing 100 mg. per kilogram of body weight of tribro-

methanol. With the patient on the left side, four-fifths of the solution, *i. e.*, 80 mg. per kilogram is introduced into the rectum through a catheter. If at the end of 6 minutes the action of the drug is not well evidenced, one-half of the remaining solution, *i. e.*, 10 mg., is then given. If the patient reacts to supra-orbital pressure after 15 minutes the final 10 mg. per kilogram is administered. Reaction to pin prick at the site of the lumbar puncture is a good test for operability of the patient.

With narcosis established, the patient is transferred to an operating table, placed on his side with the head slightly elevated and the buttocks at the break in the table. The operator then proceeds with the lumbar puncture. While oxygen is being injected the anesthetist gradually elevates the head of the table until the patient is in the sitting position. In this position the gas is distributed throughout the ventricles by manipulating the head in various planes. The body is then inclined to the opposite direction for a short while. Various amounts of gas are injected, depending on the size of the patient and the size of the ventricles. Following the introduction of the gas, the patient is transferred from the operating room for x-ray on a stretcher with the head slightly elevated. Observations on the pulse, respiration, blood-pressure, etc., are to be made throughout the procedure and until the patient regains consciousness.

The average length of sleep was from 5 to 7 hours in the cases in which the method was employed by Lessinger. Although there was a slight fall in blood-pressure, and minute volume respiratory exchange was always diminished, in no case did the patient present alarming signs or symptoms. The blood-pressure usually rose during the injection of the oxygen. Only 3 patients showed definite evidence of shock during the procedure, and only 1 case vomited in the entire series.

**CARBON-DIOXIDE ABSORPTION TECHNIC.**—This method of administration of inhalation anesthetics has probably spread in popularity with greater rapidity than any comparable technic. R. M. Waters (Ann. Surg. 103:38 (Jan.) 1936) describes the fol-

lowing conditions pertaining to inhalation anesthesia prior to its advent:

"A completely open technic, was known to result in a cold dry atmosphere being inhaled, resulting in irritation of membranes and resultant hyperactive breathing. Control of some patients was difficult or impossible. It had also been noted that excess loss of carbon dioxide with such technic sometimes caused circulatory depression (ether shock).

"A semiclosed technic was as a rule less damaging to the patient but required much clinical judgment in its use. Respiratory movements were excessive due to retained carbon dioxide. Cost of gas anesthesia, though less than with completely open technic, was for many cases prohibitive.

"With all inhalation anesthesia, sweating was the rule, reduction of body temperature usual, annoyingly hyperactive breathing frequent, and operating teams were constantly exposed to high concentrations of agents used."

Waters, following Jackson's laboratory experimentation with the absorption of expired carbon dioxide by alkali, applied the method clinically, and has had the greatest amount of experience with it. He states it has exhibited the following beneficial characteristics:

"With a completely closed respiratory system and the absorption of carbon dioxide, the vapor of agents such as ether could be inhaled in a warm and moist atmosphere. The body temperature of patients subjected to long periods of anesthesia need no longer be expected to become depressed. Irritation and stimulation of the respiratory tract was less, resulting in quiet breathing during operation. Reflex stimulation of perspiration from cold inhalations was less frequently seen, which, taken together with the maintenance of a completely moist atmosphere for inhalation, resulted in

considerable reduction in invisible water loss during the following operations. Quieter respiratory activity resulted in a decreased amount of work being performed during anesthesia. With the resultant decreased demand for oxygen, a greater margin of safety was made available in anesthesia with certain gases. The technical difficulties of administration were, in the main, simplified. The quantity of anesthetic agents used was greatly reduced. The anesthetist no longer need choose one anesthetic agent for private patients and another for ward cases on the ground of a difference in cost. The atmosphere of operating rooms was no longer saturated with anesthetic gases and vapors. Fire and explosion hazards were thus greatly reduced and surgical teams found themselves free of the chronic effects of ether and other drugs."

Two mechanical methods may be employed. First, for the closed circle type, a circle device may be used in which the expired atmosphere is carried from a face mask through tubing leading to the absorber, thence to a breathing bag or spirometer, and thence back through tubing to the mask. Somewhere along this circuit, an inlet is provided for the original filling of the system with anesthetic mixture and the constant addition of oxygen to replace that used from the mixture by the metabolic activity of the patient.

The *disadvantages of the closed circle absorber* are (1) the difficulty of eliminating leaks and (2) possible resistance to respiration by one-way valves and tubing.

The second mechanical solution of a closed respiratory system, a direct or to-and-fro application, although it has not been applied to metabolism apparatus, has proved most satisfactory in the author's hands for use under operating-room conditions in anesthesia. The arrangement is as follows:

A canister of soda lime granules (4 to 8 mesh) contained in a cylinder (8 by 12 cm. inside dimension) is inserted between a face mask and small rubber breathing bag (10-inch). Contact is made with mask and bag by means of metal tubing (2.8 cm. in diameter) in the form of easily connected and disconnected slip joints. The granules are held in place in the cylinder by means of a wire gauze dam at each end. A nipple is provided in the mask through which the closed respiratory system is filled during induction of anesthesia, and a constant measured flow of oxygen maintained at a rate of 200 to 400 c.c. per minute throughout the administration. Since there is at present a likelihood that even the best soda lime may contain dust, forceful blowing through the canister before attaching it is essential until all dust is expelled. The use of full-size bed pillow for the patient is essential. Thus provided, and with the patient's head slightly turned to the right, the lower end of the canister rests on the pillow as the mask is fitted to the face, the bag extending over the end of the pillow and the side of the operating table. The presence of the breathing bag in the immediate vicinity of the head is considered a safety factor. It is readily visible and available for artificial respiration in an emergency. If excess carbon dioxide in the anesthetic atmosphere is indicated, the canister may be omitted, the slip joints serving to connect mask to bag directly. Rarely do we find the addition of carbon dioxide to anesthetic mixtures to be advisable during maintenance. The bag and mask without soda lime are, however, often used to hasten induction time with ether and to facilitate intubation for endotracheal anesthesia. The writer believes that the addition of carbon dioxide to anesthetic mixtures in open and semiclosed technics, the excessive employment of rebreathing, and the ill-advised use of soda lime "cut outs" in closed technics have frequently resulted in physiologic damage and even fatality.

In the closing discussion it was emphasized that, in contrast to general impressions, the technical difficulties of the absorption technic are not very great; on the contrary, at the end of a month, during which it has been taught to the internes, better work is done by them with this method than with the open technic.

**DIVINYL ETHER.**—Although promising claims have been made for divinyl ether, its use is apparently spreading quite slowly, as shown by conflicting reports in the literature. According to R. M. Waters (J. Indiana M. A. 28:650 (Dec.) 1935), the first modern reference to divinyl ether, now marketed as *vinethene*, was made by Leake in 1930. He chose this ether from the derivatives of a number of higher alcohols because of its structural similarity to ether on the one hand and to ethylene on the other. Suffice it to say that work has been done on this agent by Leake, Guedel, Ravdin, Bourne and others. The reports vary widely in opinion. In offering his own experiences with divinyl ether, he states that the preparation of the drug furnished him in Madison and administered to animals in Madison does not impress him as a valuable contribution to anesthesia. When administered to dogs, the majority of animals failed to show true anesthesia with good muscular relaxation even when the concentration of the vapor in the inspired air was raised sufficiently to approach an irreversible dosage. In many dogs running movements persisted even when respiration was extremely depressed. These muscular manifestations were not seen when vinethene was administered to a few clinical patients; nevertheless, no advantage has been noted over ethyl ether. The odor is quite as distasteful and, although the induction of unconsciousness is slightly more rapid than with ethyl ether, the resulting anesthesia, both from the standpoint of the surgeon and anesthetist, has in the author's hands been distinctly unsatisfactory.

On the other hand, W. Bourne and B. B. Raginsky (Brit. J. Anæsth. 12:62 (Jan.) 1935) show that divinyl ether, when properly administered, does not, as previously suspected, alter liver func-

tion. Experiments have shown that vinyl ether anesthesia in normal dogs does not alter the liver function appreciably. In those cases in which cyanosis is a feature of the anesthesia, moderate liver damage occurs, which is not due directly to the drug, but to the associated anoxemia. It does not enhance the liver function damage produced previously by the inhalation of chloroform, nor does it delay the period of recovery from this damage. Its effect on the liver function in partially starved dogs is not appreciably different from that produced in normal animals.

In recommending the use of vinyl ether in *obstetrics* W. Bourne (J. A. M. A. 105:2047 (Dec. 21) 1935) states that it apparently does not cause liver damage nor does it interfere with muscular activity in the intestine and in the uterus.

It seems to be particularly suitable for obstetric anesthesia in general practice on account of its safety for mother and child, its ease of administration, the rapidity of its action, the satisfactory maintenance of any desired degree of narcosis, and the early uneventful recovery.

Although vinyl ether may be given with relative safety by the "open drop" method, it is preferable to administer it in a "closed" manner with oxygen.

**INTRAVENOUS ANESTHESIA.**—For intravenous anesthesia, J. S. Lundy, R. M. Tovell and E. B. Tuohy (Proc. Staff Meet. Mayo Clin. 11:421 (July 1) 1936) finds sodium l-methyl butyl thiobarbituric acid (*pentothal sodium*) a satisfactory agent. He finds that the intravenous method of anesthesia with pentothal sodium has become increasingly popular. Patients are enthusiastic about the method and the anesthetist is keenly interested in it because it permits a fine degree of control over the dosage. Pentothal sodium has

been used practically exclusively during the last year for producing intravenous anesthesia. This drug is a soluble barbiturate which produces rapid anesthesia of short duration with fair surgical relaxation and a minimum of post-operative restlessness. The writers have found that it is approximately 30 to 50 per cent. more potent than "evipal soluble."

**Indications.**—Intravenous anesthesia is being used now chiefly for surgical procedures which do not require more than 15 to 25 minutes and when complete muscular relaxation is not entirely essential. It has been used, however, in certain cases in which the indications warranted its administration for longer periods of time, *e. g.*, for as long as an hour. This method of anesthesia is useful for operations in which it is desirable that the anesthetist be out of the operative field, such as for *operations on the head and neck*. In a few instances the method has proved valuable in *laparotomies* when the general condition of the patient militated against the use of either spinal anesthesia or general inhalation anesthesia.

**Contraindications.**—As a general rule, it has been found that children 10 years of age or less do not tolerate well the intravenous administration of barbiturates on account of the marked respiratory depression which results. In addition, there are certain patients with evidence of pulmonary disease, such as basal râles or dyspnea caused by a systemic or respiratory disease, who should not, as a rule, be given intravenous anesthesia.

**Precautions.**—Ambulatory patients who are to undergo intravenous anesthesia should be attended by a responsible person if they are to be sent home following operation, since they are usually in a mild state of inebriation during the period of recovery. It is unwise to use

intravenous injections for varicose veins because there is a definite tendency toward stasis of the drug and consequent danger of absorbing all of a given dose at one time. During the course of administration of the anesthetic the patient's jaw should be watched closely by a competent attendant so that the airway may not become obstructed. In addition, oxygen and carbon dioxide should be available in case serious respiratory depression occurs. In a few cases the writers have found a Magill intratracheal tube helpful in providing an adequate airway when obstruction or dyspnea occurred.

**Administration.** — Pentothal sodium is supplied in ampoules containing 15 grains (1 Gm.) and when dissolved in 20 c.c. (5 drams) of triple distilled water it forms a clear yellow solution of 5 per cent. concentration, each cubic centimeter of which contains  $\frac{3}{4}$  grain (50 mg.) of the drug. The use of this more dilute solution has eliminated the disagreeable symptoms associated with extravenuous injections of the 10 per cent. solution. Respiratory stimulants such as "coramine" or picrotoxin may be added to the mixture in order partially to counteract the respiratory depressive action of the barbiturate, if that is deemed advisable. In order to indicate the efficiency of respiratory exchange a cotton butterfly is placed on the upper lip and nares by means of adhesive tape. This will serve as an efficient guide when respirations are shallow.

There are certain rather important points to be considered in the use of the intravenous method of anesthesia. The needle should not be too small; one that is less than 20-gauge is not satisfactory for the technic recommended. An initial dose of  $1\frac{1}{2}$  to 3 grains (0.1 to 0.2 Gm.; 2 to 4 c.c.— $\frac{1}{2}$  to 1 dram) is injected intravenously fairly rapidly while the patient counts

aloud. Usually in 10 to 15 seconds anesthesia will be established. If no more than 3 grains (0.2 Gm.) are given intravenously, the patient will recover quickly. To maintain anesthesia, the needle is left in the vein and pentothal sodium is administered in intermittent doses of 0.5 to 1 c.c. (8 to 16 minims) until 15 grains (1 Gm.) has been given. Occasionally doses of 1 to 2 Gm. (15 to 30 grains) have been used in selected cases. The rapidity with which consciousness is regained is directly proportional to the amount of drug administered, and after a dose of 10 grains (0.65 Gm.) the average adult usually regains consciousness within 10 to 12 minutes. For the average adult the writers have found that preliminary medication consisting of  $1\frac{1}{2}$  grains (0.1 Gm.) of pentobarbital sodium (nembutal), given orally, and  $\frac{1}{6}$  to  $\frac{1}{4}$  grain (0.01 to 0.016 Gm.) of morphine sulphate, administered hypodermically 45 minutes before the operation, reduces the amount of intravenous anesthetic needed.

In an analysis of the cases in which intravenous anesthesia with pentothal sodium was employed during the past year, it will be noted that its use has definitely increased for *operation on the head and neck*; previously, intratracheal anesthesia was the method of choice for this type of operation. Sodium amytal has been used intravenously because of its prolonged effect and its usefulness in medical and surgical cases for the control of *convulsions* or certain *manic conditions*. In addition, it has been of benefit in producing *rest* in cases in which patients are refractory to opiates or to other forms of narcotics.

Recently, the short-acting barbiturate, pentothal sodium, has been given to determine the degree of fall in blood-pressure in cases of *hypertension*, and it has been possible to predict fairly

accurately by this means the results that could be obtained by bilateral resection of the splanchnic nerves, first and second lumbar ganglions, bilateral partial resection of the celiac ganglions and suprarenal glands.

T. W. Pratt, A. L. Tatum, H. R. Hathaway and R. M. Waters (*Am. J. Surg.* 31:464 (Mar.) 1936), in reporting a small series of cases with pentothal sodium in a preliminary experimental and clinical study, warn (1) that it should be administered by a capable anesthetist who is equipped to cope with problems involving an oxygen and carbon dioxide imbalance; (2) that being a nonvolatile substance, pentothal sodium is not controllable, but as it is broken down so rapidly in the body, it closely approaches the actions of a controllable anesthetic agent; (3) that being a barbituric acid derivative, it is essentially a hypnotic and not an analgesic drug; (4) finally, on the basis of this small series of cases, it is felt further investigation of pentothal sodium is warranted, as it produces a short period of satisfactory anesthesia with a relatively prompt complete recovery.

**SPINAL ANESTHESIA.**—The combination of pontocaine in glucose is recommended by L. F. Sise (*S. Clin. North America* 15:1501 (Dec.) 1935) for prolonged spinal anesthesia. He points out the generally accepted thought that procaine is probably the safest and best of the local anesthetic drugs, but that for spinal anesthesia it has the great disadvantage of limited duration of action. In suggesting pontocaine, he claims as advantages its length of action (2 hours or more) and lessened depression as compared to procaine. He sees as disadvantages to its use the difficulty of controlling the height of anesthesia with the drug as supplied, and its prolonged action if inadvertently it is placed too high. To overcome these features he

DOSES OF PONTOCAINE IN MILLIGRAMS  
FOR ADULTS

|   |    |    |    |
|---|----|----|----|
| Anus.....   | 6  | 7  | 8  |
| Perineum—external genitals or<br>bladder .....    | 10 | 12 | 14 |
| Legs to groin, or pelvis (intra-<br>vaginal)..... | 10 | 12 | 14 |
| Inguinal hernia or appendix....                   | 12 | 14 | 16 |
| Lower abdomen. . . . .                            | 14 | 16 | 18 |
| Upper abdomen.....                                | 14 | 17 | 20 |

Smaller doses for older, weaker, smaller individuals.

Middle doses for 40 years, 140 pounds, and fairly good vigor.

Larger doses for younger, vigorous, larger individuals, or for especially long anesthesia.

All doses will give 1½ hours' to 2 hours' anesthesia. Doses are for the average of the 3 groups rather than the extremes, so smaller doses should be reduced for the especially frail, and the larger ones may be increased for the especially vigorous, but probably to not over 25 mg. (⅓ grain) in any case.

Anus, perineum, etc., may be done by simple dilution with spinal fluid. In higher anesthetics it is best to use 10 per cent. glucose, equal parts if the patient is to be level, and one-half as much glucose solution as pontocaine solution if patient is to be in Trendelenburg position.

suggests the following technic: No technic for placing a spinal anesthetic can be presented which will give satisfactory anesthesia in all cases. Considerable variations in method must be made for differences in individual patients, for the elderly and weak as contrasted with the young and strong, for variations in length of operation as well as in the length and curves of the spinal canal, etc. This should constantly be borne in mind in applying any given technic. It is that which brings into play the experience and judgment of the physician and which makes the average of successful anesthetics higher in one series than in another. This point is worthy of emphasis, as its disregard, with a mechanical adherence to any fixed standard, no matter how good, will be almost sure

to bring disappointment if not actual danger. A standard of technic, however, should be presented, which will fit that mythical person, the average adult, and which will serve as a base from which excursions can be made in either direction. Such a standard technic is therefore herewith presented, suitable for abdominal anesthesia in, *e. g.*, a man of fairly good vigor, about 40 years of age, weighing about 140 pounds, and of ordinary normal build. No attention is paid here to details, such as premedication, sterility, etc. Only factors bearing on the placement of anesthesia are considered. In the above table will be found some suggestions as to dosage of the drug. These also must be considered as a general guide, from which variations can be made to advantage.

1. *For Operation in Level Position.*—The dose of pontocaine solution is drawn into the syringe. (The writers use a 5 c.c. all-glass syringe.) There is then also drawn in an equal amount of 10 per cent. glucose solution, such as is commonly on hand in most hospitals for intravenous use. Thus, if the dose is to be 16 mg. ( $\frac{1}{4}$  grain) of pontocaine, then 1.6 c.c. (26 minims) of the 1 per cent. pontocaine solution is drawn into the syringe, followed by 1.6 c.c. (26 minims) of the 10 per cent. glucose solution, giving 3.2 c.c. (52 minims) of total fluid. The two solutions are then thoroughly mixed by tilting the syringe, with an air bubble within, back and forth. If the dose of pontocaine chosen is small in proportion to the field to be covered, then the proportion of glucose should be somewhat higher. If, for instance, 14 mg. ( $\frac{1}{5}$  grain) of pontocaine were to be used for a high abdominal anesthesia, then after drawing 1.4 c.c. (22 minims) of the solution into the syringe, it would be well to use glucose solution up to a total of 3 c.c. (48 minims).

With the patient in the lateral decubitus, level, puncture is then made in the third lumbar interspace. (The writers use a number 21-gauge gold needle.) The table is tilted to a 10-degree angle with the head down, a small amount (about  $\frac{1}{4}$  c.c.) of spinal fluid is drawn into the syringe, and the contents are slowly injected, at not over  $\frac{1}{2}$  c.c. (8 minims) per second. The patient is then turned on the back

and a good-sized pillow or pillows inserted under the head and shoulders so as to give as marked a bend as possible upward at this point. The patient may now be left in this position while various adjustments are being made. The first adjustment should be the position of the pillow under the back, it being placed somewhat low for a mid-abdominal operation and higher for a high-abdominal operation, while for a stomach operation it should be barely under the shoulders at all, but the pillow should never be so low that the dorsal spine at some point does not press firmly on the table. At the end of  $1\frac{1}{2}$  minutes from the beginning of injection, the slant of the table is decreased until it is just a little off level, at perhaps 4 degrees slant. The position of the patient and the slant of the table should now be such that the lowest point of the spine is a little short of the segment where it is desired the upper border of the anesthesia shall be, and the spine thereafter rises at an increasing angle toward the head, effectually stopping all further progress cephalad of the heavy solution, but still allowing it to run downward toward the lowest point.

The patient should now be tested to determine the height of anesthesia. In 2 minutes from the time of injection the upper border of anesthesia will usually be found somewhere in the abdominal region between the groin and the costal margin, but will rapidly rise and in about 3 minutes will be established between the costal margin and the nipple line. The table is then adjusted slightly so that it is just off level, with the head down, and slanting about 2 or 3 degrees, when the surgeon may proceed.

While in most instances the progress of events is as described, yet there are sometimes considerable variations. In a few instances the anesthesia may run up very rapidly and get a little too high, and sometimes it may move but slowly and reach sufficient height only with some difficulty.

If it gets too high it does so only by a small margin if proper position has been maintained, as further upward progress is definitely stopped by the upward curve of the spine at the shoulders and neck. In such a case it is well to raise somewhat the head of the table for about 5 minutes, in order to lessen the intensity of the anesthesia at its upper border, when the table is again put back approximately level. During any period when the head is up the patient should be watched carefully for symptoms of cerebral anemia.



The most frequent difficulty, however, is that the anesthesia does not rise fast enough or go high enough. This may usually be remedied by tipping the head of the table down again to a 10-degree slant or even more. The length of time after which the anesthesia may be moved by changing the position of the patient varies directly with the size of the dose used, but is usually around 5 to 15 minutes, so that, as a general rule, if the anesthesia is not well into the abdomen in 3 minutes or approaching its goal in 4 minutes, steps should be taken to speed it along. The amount of tilting of the table and the length of time it is kept down are roughly proportioned to the gap shown between the actual and the desired heights of anesthesia. It must be remembered, however, that the patient should not be left in more than a little head-down slant for many minutes without being leveled up and tested for height of anesthesia.

2. *For Operation in Head-Down Position.*—If the head-down position is to be preceded by some other procedure, as, for instance, if a hysterectomy in Trendelenburg position is preceded by a perineorrhaphy and perhaps trachelorrhaphy, the technic for patient level, above described, may safely be employed, as the anesthesia becomes well stabilized before the Trendelenburg position is assumed; but where the head-down position must be assumed early, say within the first 15 minutes, as in a simple hysterectomy, then anesthesia under the above technic might go too high. Here the technic is as follows:

The amount of 10 per cent. glucose solution is reduced to half the amount used in the first technic. Thus if 16 mg. ( $\frac{3}{4}$  grain) is the dose selected, 1.6 c.c. (26 minims) of the 1 per cent. pontocaine solution is used and 0.8 c.c. (13 minims) of the 10 per cent. glucose. After these have been thoroughly mixed, they may be used in the same manner as novocaine, either in 10 per cent. solution or as crystals dissolved in spinal fluid, in any of the ordinary methods commonly in vogue. The method most commonly used by the writer is to dilute this mixture with spinal fluid to a total of 5 or 6 c.c. and inject in the third lumbar interspace at 0.5 c.c. (8 minims) per second in 5 to 10 degrees head-down slant. During the next 10 minutes, the slant of the table is adjusted according to the progress of the anesthesia. If this appears to be rising too rapidly and too far, the table is leveled up, for a time, but if the anesthesia is too low, the table is left down or is even increased in

slant, for gravity still has its effect in this technic, just as it does in the common methods in vogue with novocaine, though this effect is far less marked than it is under the first technic mentioned.

*Comment.*—The first method described, for patient in the level position, depends almost entirely on gravity for its effectiveness. As the solution, markedly heavier than the spinal fluid, enters the spinal canal, it flows downward, but the result of its flow is not the simple one it would be in a smooth open tube. This tube into which it is injected is largely filled by the spinal cord and is further broken up by numerous obstructions, such as the nerve roots, the dentate ligament, and the innumerable fine trabeculae which stretch from the arachnoid to the pia. These trabeculae are so numerous as to form a veritable network or reticulum. As the mixture in its downward flow meets these various obstructions, they act on it as baffles, causing it to be mixed mechanically with the spinal fluid and diffused throughout the cross section of the spinal canal and thus causing the anterior as well as the posterior nerve roots to be thoroughly anesthetized. This fact is quite evident clinically.

This diffusion of the mixture as it flows downward steadily robs it of substance or body and attenuates it so that it might not reach far beyond the desired distance even if the downward slope continued much further. As the slope levels off, however, and finally begins to rise, further progress is very definitely stopped even if there is still some free anesthetic solution with active drug left. Here, then, is the great advantage of this method, the fact that the force of gravity constantly urges on the progress of the anesthesia toward the head until it has reached about to the desired level, when the same force first

retards and then definitely stops further progress.

Diffusion does not now carry the anesthesia higher because (1) there is probably little free drug now left at this point to diffuse, and (2) diffusion under these circumstances is so slow as to be negligible, as has been shown repeatedly since the time of Barker.

About the second method, that for patients operated upon in the head-down position, little need be said. It is about on a par with methods commonly in vogue for novocaine and lacks the speed, accuracy and definiteness of the first method. It has, however, the various advantages which pontocaine has over novocaine, which were mentioned early in this article.

It may be said that there is one distinct objection to the first method. Suppose a gall-bladder operation is started under this anesthesia and the blood-pressure falls markedly. If the patient is put in the Trendelenburg position to lessen cerebral anemia, will not the anesthetic solution then run dangerously high? To such a query two answers may be made:

1. If there has been no marked error in judgment and the patient is therefore in suitable condition for the operation and for spinal anesthesia, a lowering in blood-pressure sufficient to dictate a material lowering of the head should not occur.

2. Should an error of judgment be made in choosing this form of anesthesia and should a marked drop in blood-pressure therefore occur, the head of the table may still be lowered sufficiently for practical purposes. As far as the circulation is concerned, a marked slant is not necessary, and with stout patients at least, it is not desirable. A 5-degree slant is probably enough to maintain cerebral circulation at least till other

measures such as adrenalin, oxygen, etc., can be used. Moreover, the dose of pontocaine is so small, even for a long and widespread anesthesia, that practically all of it is soon fixed in the tissues (and/or absorbed?) and the amount left free, if any, is so small that no harm is done by change of position. Certain clinical experience to date agrees with these assumptions.

The results of use of this method indicate that the technic described for patients level is the most rapid, accurate, and safe one which has yet been employed and that the technic for patients in head-down slant is about on a par with methods commonly in use.

Sise concludes that pontocaine is a desirable anesthetic for spinal anesthesia in that it gives a sufficiently long anesthesia to cover easily all but a few exceptional operations, with less depression than where novocaine is used; though it is difficult to control in the higher anesthetics. To obviate this difficulty, a method is presented for using it in combination with 10 per cent. glucose. This method, for patients in the level position, seems to the writer to be more rapid, accurate, and safe than any other method that has heretofore been used.

**Complications.**—An excellent résumé of the complications of spinal anesthesia was reported by L. D. Orkin (Tr. Am. Soc. of Regional Anesth. (Mar. 3) 1936). The literature on the subject for the 10-year period 1925-1935 is reviewed and the reported material grouped under the various systems. On the respiratory system, he concludes, that although the opinions are divided, from statistics reported "it can be readily seen in the summary in which 11,143 cases are reviewed, that spinal injection has not in these cases prevented or lessened pulmonic complications."

*Summary.*—11,143 cases.

|                        |                |
|------------------------|----------------|
| Pneumo-lobar broncho . | 1.3 per cent.  |
| Pneumo hypos .....     | 0.24 per cent. |
| Collapse .....         | 2.5 per cent.  |
| Bronchitis .....       | 1.4 per cent.  |
| Laryngitis .....       | 1.2 per cent.  |
| Rhinitis .....         | 1.1 per cent.  |
| Cough .....            | 5.1 per cent.  |
| Pleurisy .....         | 0.4 per cent.  |
| Infarct .              | 0.4 per cent.  |

Orkin states that with regard to the central nervous system, it is definitely felt that the agents used in spinal anesthesia have toxic effects on neural tissue, but this reaction is rapidly reversible with recovery complete and rapid. However, under some conditions the toxic reactions may not regress, and temporary or permanent damage may be done as evidenced by symptomatology.

The list of complications which have been reported include excitement, paresthesias, moderate and severe headache, psychoses, myelitis, aseptic and true meningitis, ocular palsies and others, as follows:

*Summary.*—45,966 cases.

|                        |                |
|------------------------|----------------|
| Excitement .....       | 0.22 per cent. |
| Anesthesia .....       | 0.19 per cent. |
| Moderate headache .... | 11.1 per cent. |
| Severe headache.....   | 4.9 per cent.  |
| Psychoses .....        | 1.8 per cent.  |
| Myelitis .....         | 0.16 per cent. |
| Aseptic Meninges ..... | 0.26 per cent. |
| True Meninges .....    | 0.12 per cent. |
| Ocular Palsy .....     | 0.70 per cent. |
| Others .....           | 0.9 per cent.  |

With regard to the gastrointestinal system, Orkin states that comparative studies made in different clinics reveal, first, the high incidence of such complications, and, second, the fact that they may be grossly exaggerated. Summarizing the gastrointestinal complications in 4,475 cases, nausea and emesis has an incidence of 14.3 per cent. and distention is reported at 10.2 per cent. Other complications, such as gastric hemorrhage, ileus and parotitis, occur with an incidence of about 0.16 per cent. and 0.40

per cent. respectively. In reviewing the genitourinary complications in 6,162 cases, it is evident that retention is the most frequent complication, being reported at 8.1 per cent. Hematuria and nephritis are noted as 2.7 per cent. and 0.4 per cent. respectively. Other complaints comprise incontinence, cystitis and imperfect function, with an incidence of 4.5 per cent. Likewise, a review of the circulatory complications in 3,643 carefully studied cases, the incidence of shock following operation was 4.4 per cent., severe post-operative hemorrhage 1.1 per cent., and change in rate (tachycardia or bradycardia) 3 per cent. Other complaints include phlebitis and embolus, with an incidence of about 0.4 per cent.

Two reports are quoted showing that pulmonary complications (North) occur almost twice as frequently when spinal is supplemented by inhalation anesthesia, and that morbidity and mortality (Rovenstine) are almost doubled as compared to when either is employed alone. In comparing the results following intra- and extraabdominal operative procedures, it will be noted that every complication, with the exception of atelectasis which is about equal for the two groups, is markedly increased as much as 300 per cent. for intraabdominal work.

Mortality tables vary from zero to 1100 cases to 10.8 in 338. In New York City for the period of 1928-1932 there were 48 deaths on the operating table attributable to spinal anesthesia among 369 reported deaths. In a summary of 277,443 reported cases, there were 583 deaths for a fatality incidence of .18 per cent. In reviewing the figures reported in the literature for the periods of 1929-1936, there were 39,146 spinal anesthetics with 486 deaths, or a fatality incidence of 2.2 per cent. The .03 per cent. reported by Bessessen may be too low, while the 2.2 per cent. for the period

1929-1936 may be too high, but the latter represents a figure derived from statistics reported recently in which the

writers reported their results more carefully and employed more detailed follow-ups.

## BRONCHOSCOPY

By CHEVALIER JACKSON, MD., Sc.D., LL.D., and  
CHEVALIER L. JACKSON, A.B., M.D., M.Sc.

### MOVEMENTS OF BRONCHI.

So much in the literature of asthma and other supposedly spasmodic respiratory diseases is based upon assumption of bronchial movements that the researches of Maxwell Ellis (Proc. Roy. Soc. Med. 29:527 (Mar.) 1936) are of utmost importance as a good start in the direction of replacing unwarranted assumption with objectively demonstrated facts. For his researches Ellis designed a specially constructed instrument that could be inserted into any given portion of a main bronchus of a dog. The instrument is essentially a balloon for the recording of circumferential changes; it is inflated after introduction into the bronchus. The balloon is traversed by a hollow tube that extends beyond it, thus avoiding distal atelectasis or other disturbances of pulmonary function. A very sensitive volumetric method of recording with the use of a small Brodie bellows gave graphic, amplified tracings of the bronchial movements under varying conditions. Bronchial contraction was recorded after administration of pilocarpine, and transitory relaxation after injection of adrenalin. After bilateral vagotomy, bronchial movements increased, synchronously with respiratory movements. Bronchial contraction as well as an increase in the rate of respiration followed stimulation of the right nasal cavity with dilute ammonia vapor. Contraction of the right bronchial lumen was noted after stimulation of the left nasal cavity. One of the interesting conclusions reached by Ellis is that the function of the bronchial muscle is to

maintain a certain tone in the bronchial tubes, preventing their entire collapse or uncontrolled expansion; he found no experimental evidence for assigning to it a more active part. Looking at this piece of research work broadly, it seems to mark an epoch by demonstrating the great value of bronchoscopy in the study of bronchopulmonary physiology and pathologic mechanism, a value that arises particularly because of the possibility of research work without greatly disturbing normal conditions. By way of contrast, it may be stated that any research involving thoracotomy utterly precludes any possibility of study of normal bronchopulmonary mechanism.

**FOREIGN BODIES IN BRONCHI.**—E. J. Patterson (Proc. Am. Bronchoscopic Society, 1936) demonstrates the value of **costophrenic bronchoscopy** in the removal of foreign bodies at the periphery of the lung. Curiously, a number of such cases are reported in the European literature as calling for thoracotomy.

**PULMONARY ABSCESS.**—Twelve cases of acute, putrid pulmonary abscesses treated by **bronchoscopy-therapy** are reported by A. Soulas (Schweiz. med. Uchenschr. 66:609 (June 27) 1936). The abscesses had existed for from 4 to 8 weeks. From 4 to 8 treatments were given during a period of 6 to 12 weeks, with complete recovery in 75 per cent. of the cases.

**ACUTE LARYNGOTRACHEO-BRONCHITIS.**—This disease was observed and its clinical features were

very accurately described over a century ago by Bland and almost that long ago by Trousseau. It has occurred not infrequently ever since, and its mortality is high, yet it is almost entirely absent from vital statistics and many practitioners believe they have never seen a case. Clinically and statistically, it is buried under one of its terminal phases, *bronchopneumonia*. These and other facts are clearly presented, along with other data, by Chevalier Jackson and Chevalier L. Jackson (J. A. M. A. 107: 929 (Sept. 19) 1936). They describe the bronchoscopically observed living pathology, and reach the following conclusions:

1. Acute laryngotracheobronchitis is a clinical type. It occurs most often and most severely during epidemics of acute respiratory infection. In from 3 to 5 per cent. of the cases the influenzal bacillus seems to be causative; occasionally other organisms seem responsible, but over 90 per cent. of the cases are primarily or secondarily streptococcic. The mortality in children under 3 years is about 70 per cent.

2. In spasmodic croup observations of the living, pathologic conditions show that the mucosa is lavender, violet or grayish in color, but is otherwise normal, and the discoloration quickly disappears when the airway is laryngoscopically held open, without leaving a trace of abnormality. It is suggested that attacks may be due to inspiration of pharyngeal secretions during sleep. The consequent sudden and violent efforts to draw in air, draw in the abnormally flabby rachitic laryngeal orifice in a sphincteric closure.

3. In diphtheria limited to the larynx and tracheobronchial tree there is a fibrinous exudate that objectively is very different from the inflammatory exudate seen in streptococcic infection of the same mucosal areas.

4. In acute laryngotracheobronchitis the outstanding feature of the bronchoscopically observed pathology is the bronchial obstruction by inspissated secretion which the weak or absent cough reflex is unable to expel. Therefore, the following points are important:

(a) The routine administration of atropine and opium derivatives is illogical in theory and often fatal in practice.

(b) The superheating of the air in hospitals and dwellings contributes largely to inspissation of secretions. Outside air at zero contains little water, even at dewpoint. When air is heated to 70 degrees it becomes extremely desiccating to the secretions and almost caustic to the mucosa. The air surrounding the patient having laryngotracheobronchitis with inspissating secretions should be humid to saturation.

(c) In this disease an impaired percussion note and increased respiratory rate usually mean not pneumonia or bronchopneumonia, but obstructive atelectasis.

(d) These signs call for peroral or tracheotomic aspiration of secretions. In extreme cases forceps removal of crusts is the only means of saving life. Such potentially fatal circumstances can be prevented by humid air and the avoidance of atropine, opiates and other desiccating medicaments.

5. In the treatment of babies it must be remembered that, relatively, a cat in the laboratory has 9 lives; a dog about 3; but a baby in his crib has only one. It is a paramount duty of the pediatrician and the family physician to see that the baby gets intervals of rest and that such rest is not interfered with by too many examinations, by serum reactions, torturing urticaria and subdermal abscesses. This is not a criticism of scientific medicine, but a reminder to the clinicians that they are the balance wheels of the therapeutic machinery.

## CANCER

By CLARK E. BROWN, B.S., M.D.

**Etiology.**—In 1933, R. E. Shope and E. W. Hurst provided an entre for a series of basic experiments in cancer research by an unpretentious report on infectious papillomatosis in rabbits. He had learned of such a disease being endemic in cottontail rabbits of Iowa and Kansas. The horny skin lesions of these animals at times covered large bodily surfaces. Shope identified the causative agent of these papillomas as a *filtrable virus* having a marked tropism for cutaneous epithelium. The disease could be transmitted in series through wild rabbits, and to domestic rabbits. The lesions made their appearance in 6 to 12 days after inoculation. They usually persisted for many months as enlarging confluent papillomatous masses. Blood stream inoculation of the virus and subsequent sterile skin scarification resulted in papilloma formation at the injured site in a few instances.

A year later, P. Rous and J. W. Beard reported further studies with the virus. Their interest was directed to the neoplastic qualities of the papillomas in domestic rabbits. They found that these grew readily in various transplantation sites, and that the virus stimulated to growth activity only the epithelium of the skin. Over extended periods they noted blood and lymph vessel penetration, and the assumption of epidermoid carcinoma characteristics by the papillomas disturbed with Scharlach R injections. In 1935, P. Rous and J. W. Beard (J. Exper. Med. 62: 523 (Oct.) 1935) were able to report that the virus papillomas following single injections of the virus became epidermoid carcinomas in 7 of 10 domestic rabbits without the added stimulative effect of Scharlach R if they were kept more than 200 days. The fact that domestic rabbits

developed carcinomas frequently and the original cottontails only very rarely was attributed to a more favorable association between the virus and the domestic rabbit epidermal cells. Cancer could never be clinically ascertained before the fourth month after injection. The more vigorous and extensive the papillomatous growth, the more likely was the malignant change to take place; and as in cancer in general, trauma, infection and chronic inflammation had a precipitating effect. Titration of the virus by P. Rous, J. G. Kidd and J. W. Beard (*Ibid.* 64: 385 (Sept.) 1936) indicated that the more concentrated the virus used in producing certain confluent papillomas, the sooner and oftener did cancer develop compared with other areas present for the same length of time but resultant from lesser virus concentrations. It is clear that the cancers result from cells proliferating under the influence of the virus. The question which the authors ask themselves namely, "Is the virus or some variant upon it the immediate cause of cancers deriving from papillomas?" is an extremely difficult one to answer. They state, however, with justification that the virus, although heavily conditioned in its carcinogenic activity, is the nearest cause for cancer now known.

Continued chemical and biological work with the *carcinogenic hydrocarbons* has resulted in the production of a water soluble addition compound of *methylcholanthrene* and *desoxycholic acid*. This compound has been found by M. J. Shear (Am. J. Cancer 26: 322 (Feb.) 1936) to be as active in sarcoma formation as methylcholanthrene when injected into the soft parts of mice. The author credits Fieser and Newman with findings that methylcholanthrene forms

such a water soluble addition compound with desoxycholic acid in which 4 molecules of bile acid are combined with 1 molecule of the hydrocarbon. A point of morphologic significance in the paper concerns the recognition of individual cells as being malignant. Shear has noted in the developing mouse sarcomas what in fresh living tissue preparation he believes are characteristic tumor cells. These cells predominate later when the tumor becomes recognizable as malignant by the usual fixation and staining methods. This identification was possible 53 days after the injection of methylcholanthrene, at which stage the tissue was found to grow in all cases on transplantation. Strangely, even before the time of successful transplantation the author could identify these cells in fresh preparations. In this connection one cannot but think of MacCarty's oft repeated appeals for the recognition of cancerous tissue in the fresh state. The earlier diagnosis of the malignant change may come indeed from refinements in fresh tissue technic.

The nonspecificity of 1-2-5-6 *dibenzanthracene* in tumor production has been indicated by the subcutaneous injection of this hydrocarbon suspended in paraffin into mice, rats, and rabbits by C. D. Haagensen and O. F. Krehbiel (*Ibid.* 26: 368 (Feb.) 1936). The variety of tumors produced includes fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma and squamous cell carcinoma.

The carcinogenic action of hydrocarbons has been carried also into the realm of the viscera. Pellets of 5 per cent. *dibenzanthracene*, *methylcholanthrene*, and *benzpyrene* fused with *cholesterol* were introduced into the kidney, spleen, liver, uterus, testicle, bone-marrow, subperiosteum, stomach, and brain of rats and mice by F. W. Ilfeld (*Ibid.* 26: 743 (Apr.) 1936). Epidermoid carcinomas of the kidney

were produced in both rats and mice after an average of 9 months. Before the development of tumor, an inflammatory foreign body reaction took place around the pellet. In the liver, 2 tumors resulted from a fairly large series of dibenzanthracene implantations in mice. The few rats implanted were negative. One liver tumor could not be identified and the other resembled primary carcinoma. One of 20 mice developed epidermoid carcinoma of the uterus with dibenzanthracene. Methylcholanthrene produced a fibrosarcoma possibly of splenic origin. No other organs yielded tumors.

H. J. Bagg (*Ibid.* 26: 69 (Jan.) 1936) has succeeded in confirming the work of Michalowsky by producing teratoma testis in adult roosters by injection of *zinc chloride* into the testicle. Both authors report success in the spring of the year when the testes are increasing in size and functional activity. Michalowsky produced tumors only in the first three months of the year, and Bagg, after prolonged gonadotropic hormone injections, produced a teratoma with zinc chloride as late as June. The technic consisted in a single injection of 0.3 c.c. of 5 per cent. zinc chloride solution which was sometimes repeated once. Intense inflammation and necrosis of the testicle resulted. The tumors which developed were of the adult type of teratoma, showing bone, cartilage, connective tissue, muscle, fat, nerve, glands and epithelium. The tumors were of infrequent incidence, failed to metastasize, did not grow on transplantation, and did not induce detectable amounts of prolan A in the blood. Immature roosters did not develop tumors. The prolonged injection of gonadotropic hormone alone could not induce them. Tumor development is explained here by the addition of an intensely irritative factor to testicular epithelium physio-

logically hyperplastic to a critical point. Spontaneous occurrence of teratomas in fowls is very rare.

The essential characteristic of the cancer cell, as stated by A. Lacassagne (*Ibid.* 27:217 (June) 1936) in prefacing his excellent paper on the hormonal pathogenesis of breast cancer, is its "loss of subordination to the rhythm of division." This inexhaustible potency for multiplication is retained by subsequent cell generations of a cancer, and is resistant to therapeutic efforts to restore cellular subordination to the laws governing the organism as a whole. Among the factors arising within the body which influence cell multiplication are the hormones, and it is with *estrone*, a form of female sex hormone, that Lacassagne deals.

The physiologic effect of estrone on the sexual apparatus are well known. In the breast it causes dilatation and cellular proliferation of the ducts. These effects are cyclic, occurring with subsequent regression every estrus cycle. By continuous stimulation of the breast epithelium with massive weekly injections of estrone benzoate, Lacassagne has introduced a cellular disturbance which has resulted in cancer. In strains showing a high female incidence of breast cancer he has succeeded through hormonal injection in developing the breasts of male mice equal to that stage of proliferation seen in the female, whereupon the incidence of carcinoma becomes the same in both sexes. Under normal conditions, males of the strain rarely develop breast cancer.

To eliminate any hereditary factor, the experiment was repeated on a strain of females, only 2 per cent. of which die of breast adenocarcinoma. The injections were begun shortly after birth. At the eighth month, when almost all the mice of the high incidence strain had died of adenocarcinoma of the

breast, these animals showed no growth. In the next 9 months, however, under continued hormonal stimulation, all the mice of this strain succumbed with adenocarcinoma of the breast. Lacassagne is now continuing his hormone injections into female mice of a strain which has never been known to develop breast carcinoma. So far, no cancers have been produced although 5 have passed the twelfth month. The author substantiates the fact that 2 factors are operative to produce breast cancer, *i. e.*, the hereditary and hormonal factors, and points out that the hereditary element operates through an unequal response of the same organs in different strains to the same quantity of the hormone. In the susceptible strains of males the proliferative element develops earlier and far outstrips that in the resistant strains. These differences are also reflected in the genital apparatus.

Lacassagne suggests *hormonal retention* in the breast as a provocative element, and theorizes upon the possibility of transformation of estrone into one of the carcinogenic hydrocarbons.

The frequency of mammary cancer in mice has no constant relation to the duration of estrus or to the average number of estrus cycles in various strains of mice. E. L. Burns, M. Moskop, V. Suntzeff and L. Loeb (*Am. J. Cancer* 26:56 (Jan.) 1936) observed 10 strains of mice which had characteristically varying indices of mammary cancer, and noted seemingly constant strain differences in the sexual cycle. The latter, however, did not parallel the former in any way, allowing the conclusion to be drawn that hereditary breast cancer in mice is not the result of an inherited influence on the frequency and duration of the sexual cycle.

**Pathology.**—In order to arrive at a just medico-legal decision on the relation between *trauma* and the subsequent



development of cancer J. Ewing advises the satisfaction of 5 requirements. These are (1) authenticity and adequacy of the trauma; (2) previous integrity of the wounded part; (3) origin of the tumor at the exact point of injury; (4) reasonable time limit between the injury and appearance of tumor; (5) positive diagnosis of the presence of tumor, and of its nature. In cases of bone tumor, the relation of single trauma to subsequent tumor is most clear cut.

In 375 *prostates* recovered from autopsy material, R. A. Moore found 52 to contain carcinomas not recognized clinically. In only 10 of these was a gross diagnosis possible. There was no direct connection demonstrable between benign hypertrophy and the development of carcinoma.

R. M. Entwisle and J. A. Hepp have reported the development of gynecomastia, lactation and positive Aschheim-Zondek reaction in a 22-year-old male with *chorionepithelioma of the testis*. Such evidence for the sex nonspecificity of hormones is important.

As a sequel to a discussion of the feminizing effects of teratomatous tumors in the male, a paper concerning *adrenal cortical tumors* by H. Lissner (Endocrinology 20:576 (July) 1936) is of interest. He selects 3 cases from the literature and presents one of his own in which the male patients developed gynecomastia, lactation, loss of potency and testicular atrophy. In one case there was a return to normal following removal of an adrenal cortical tumor. In contrast to these is the more common masculinizing influence of similar tumors in the female. Such a case of an adult woman with adrenal carcinoma who developed hypertension, obesity, virilism, hirsutism, a coarse voice, and an acneiform eruption, is reported by R. J. White (Am. J. Surg. 32:347 (May) 1936). In female children hirsutism and

masculinization are pronounced. The mode of interference of the cortical adrenal tumors with the normal interplay of sex factors is unknown. Three explanations for the rôle of the adrenal tumors have been offered by White: (1) Indirect action of adrenal on the gonads; (2) retention of the primitive sex function by the adrenal tumor cells; and (3) adrenal stimulation of the anterior pituitary with subsequent gonadal response.

A hint of the function of the interstitial cells of the testis is given in the rare cases of tumor arising in these cells. C. A. Stewart, E. T. Bell and A. B. Roehlke (Am. J. Cancer 26:144 (Jan.) 1936) report such a tumor causing hypergenitalism in a 5-year old boy. Premature pubertal transition and hypergenitalism are the effects of these tumors in children. Only 3 interstitial cell testicular tumors in boys have been reported.

A detailed study of the *anemia of malignant disease* is wanting. It has been undertaken by T. R. Waugh (Am. J. M. Sc. 191:160 (Feb.) 1936). He divides the causes into primary and secondary, the former concerning the hemopoietic deficiency brought about through direct action of the cancer cells or their metabolites on bone-marrow, and the latter affecting the blood-forming organs indirectly. Examples of the types of secondary or indirect causes are hemorrhage from the stomach, rectum or uterus involved in growth; interference with gastric function by tumor replacement; or a hemorrhagic diathesis developing from a tumor causing obstructive jaundice. Cachexia is an unsatisfactory explanation of the primary causes. Phagocytosis of the red cells by tumor cells is untenable, and mechanical disturbance of the marrow by tumor cells is unlikely in early invasion. Resort to toxic effects of tumor cells on the blood-forming foci has been taken,

but specificity as to the nature of the toxic effect has been lacking. To emphasize what a study of these anemias may reveal, the author reports 2 cases of hemolytic anemia occurring in metastatic osseous carcinoma. He suggests some fundamental alteration in hemopoietic activity incident upon the carcinomatous invasion of bone.

**Diagnosis.**—R. B. Greenough has outlined a good plan to follow in the management of a woman with a suspicious lump in her *breast*. He emphasizes very properly the fact that in every woman over 20 with a lump in her breast the possibility of cancer must be considered, and that *exploratory operation* should be the next logical step. The exploration should be performed so that adequate exposure of tissue for gross and microscopic examination is accomplished with minimal risk of dissemination of the growth. The exploration should not be performed until preparation for radical operation, in the event of necessity, has been made. After removal of the suspicious lump, the wound is packed with 10 per cent. formalin gauze and a frozen section is performed. If the diagnosis of malignancy is established, the wound is closed over the gauze, the instruments, gloves, etc., are discarded, and a **radical mastectomy** is accomplished without further delay. Such a procedure will undoubtedly increase the rate of cure of breast cancer, because it establishes a definite diagnosis at once and avoids costly treatment.

Certain significant points of practical importance in *bone tumor* diagnosis have been discussed by C. C. Simmons. He pointed out that osteogenic sarcoma usually affects the epiphyseal ends of long bones in young people. In bone tumors of persons over 50, tumors such as lymphoblastoma, metastatic carcinoma, myeloma, or hypernephroma should re-

ceive prior consideration. The latter group calls for palliation and not amputation. Malignant bone tumors do not occur in the phalanges. Osteogenic sarcoma is the most common tumor of the upper end of the humerus. The one benign tumor most commonly confused with sarcoma in this site is giant cell tumor which has a characteristic x-ray appearance and is usually cured by curettage. The x-ray features suggestive of *osteogenic sarcoma* are as follows: (1) situation of the tumor; (2) it is both osteoplastic and osteolytic; (3) the shaft outline is preserved within the tumor; (4) tumor outlines not sharply defined; (5) presence of reactive angle where tumor joins cortex; and (6) sun-ray appearance of bone spicules beneath periosteum.

The *giant cell tumor* shows a sharp outline, usually expands the cortex, and may enter the joint because of its association with cartilage.

Ewing's sarcoma often arises in the shaft of long bones and in flat bones, although osteogenic sarcoma is sometimes also seen in the shaft of the humerus.

Chondromas, although benign, should be **removed** because of their tendency to malignant change. It should be remembered that the commonest bone tumor in patients over 50 is *metastatic cancer*.

The necessity of *biopsy* for preoperative diagnosis in suspected malignancy is recognized by surgeons and radiotherapists as well. With the increasing utility of biopsy, various technical methods of obtaining the specimen have come to hand. For the purpose of comparing the advantages and disadvantages of each method, the American Radium Society held a symposium at which were presented the following, "Incisional Biopsy," "Advantages and Limitations of Aspiration Biopsy," and "Electrosurgical Biopsy."

J. M. Hanford and C. D. Haagensen (Am. J. Roentgenol. 35:238 (Feb.) 1936) state that *incisional biopsy* with a fine sharp scalpel gives the best specimen for the pathologist, with the least risk for the patient. They point out the disadvantage of distortion of normal cell relationships by both the aspiration and electrosurgical methods. Such distortion, however, is not complete. The valid objection to the aspiration method is raised, in addition, that small cancers may be missed in deep tissue.

The chief indication for *aspiration biopsy* as proposed by H. E. Martin and F. W. Stewart (*Ibid.* 35:245 (Feb.) 1936) is to obtain a specimen from tumors lying below the surface, thereby circumventing the necessity of incising normal tissue to reach the growth. Also the simplicity of such a technic requiring only local anesthesia, saves the patient time and expense of a formal operative procedure. The risk of post-operative wound break-down by tumor and infection is minimized. In advanced or extensive deep tumors, where formal procedures are unwarranted to obtain a specimen, aspiration will readily secure material sufficient for diagnosis. In doubtful breast cancer when preoperative irradiation is to be used, aspiration is the method of choice. On the other hand, many times only a diagnosis of benignity or malignancy can be given. Interpretation of the meager distorted cell patterns requires more experience than the usual hospital pathologist can attain readily in handling routine material.

The advantages of *electrosurgical biopsy* as presented by G. E. Ward and C. F. Geschickter (*Ibid.* 35:248 (Feb.) 1936) are the obtaining of sizable pieces of tissue from vascular areas, bloodless removal of precancerous areas without fear of dissemination, sterilization of the incisional line by heat, and sealing lymphatics and capillaries. These latter

advantages are probably theoretical only. The chief objection to the method comes from the pathologist who finds insufficient undistorted material left for diagnosis if only small fragments are removed.

Each method undoubtedly has its place. The REVIEWER cannot agree with the belief expressed by the aspiration biopsy proponents that preoperative aspiration biopsy is preferable to a frozen section during operation. Too often the microscopic architecture of a specimen is essential.

One possible utilization of Berger's measurement of the *electrical activity of the human brain* has been demonstrated in the localization of *cerebral tumors* by W. Grey Walter (Lancet 2:305 (Aug. 8) 1936). Berger, in 1929, by means of a galvanometer or amplifier and oscillograph, was able to elicit outside the skull waves (alpha waves) having an amplitude of 10-100 microvolts and a frequency of about 10 cycles per second. These waves were found to vary among individuals, but to be fairly constant per individual. Since they were inhibited by visual or mental activity, and since there was some evidence to point to their origin in the occipital cortex, they were thought to indicate physiologic rest in a cortical area associated with one function. The earlier work was concerned mostly with epilepsy and anesthesia.

The author, at the suggestion of F. J. Golla, applied *electroencephalography* to brain tumors. It was found in preliminary work on a few cases that records obtained from the skull leads closely resembled those obtained directly from the brain at operation. General anesthetics and increased intracranial pressure induced disturbances in the waves. In 4 verified cases of brain tumor in which the cortex was involved by invasion or affected by proximity, slower waves of lower potential than

normal were recorded from the skull. No localizing wave differences were found in 3 cases in which the tumor was deep in the cortex or below the tentorium. No false positives have been encountered so far. The author, however, states that the method, although promising, can be considered only as a supplementary procedure to clinical and radiological technics.

**Prognosis.**—The importance of delay and the inevitability of spread of *breast cancer* are emphasized by the fact, that in a group of 159 patients, those without axillary metastasis showed a median duration of 3 months, while those with axillary metastasis showed 6 months median duration. These figures reported by C. C. Simmons, G. W. Taylor and H. D. Adams (New England J. Med. 215: 521 (Sept. 17) 1936) become more emphatic when it is pointed out that a breast cancer patient without axillary involvement has 3 chances in 4 for cure, and the patient with axillary metastasis has only 1 chance in four. In this comparatively small series the 5-year cure rate is 43 per cent.

An attempt to ascertain the value of preoperative prophylactic irradiation in breast cancer was made in a series of 94 consecutive cases. The cases with axillary metastasis were distributed equally in each group. Preoperative treatment consisted in 4 exposures on successive days totalling 800 r. This was given to half the patients. The percentage cures of 77 per cent. without glandular involvement and 25 per cent. with glandular involvement were practically the same regardless of whether preoperative irradiation was given.

An index of the late results of major intracranial operations for *brain tumor* is to be found in excellent summary in a table drawn up by H. Cairns (Lancet 1: 1223 (May 30) 1936). The material for this report consists of 157 brain

TABLE

| Type                    | Died in Hospital | Died Subsequently | Still Living 7-9 Years After Operation | Total |
|-------------------------|------------------|-------------------|--|-------|
| Glioma.....             | 11               | 40                | 8                                      | 59    |
| Pituitary adenoma...    | 1                | 9                 | 19                                     | 29    |
| Meningioma...           | 5                | 8                 | 18                                     | 31    |
| Neuroma (acoustic)...   | 1                | 1                 | 8                                      | 10    |
| Craniopharyngioma.....  | 2                | 2                 | 1                                      | 5     |
| Cholesteatoma.          | 0                | 0                 | 2                                      | 2     |
| Blood-vessel tumor..... | 1                | 0                 | 3                                      | 4     |
| Metastatic tumor.....   | 1                | 7                 | 0                                      | 8     |
| Granuloma...            | 0                | 2                 | 1                                      | 3     |
| Miscellaneous.          | 0                | 3                 | 3                                      | 6     |
| Total.....              | 22               | 72                | 63                                     | 157   |

tumors treated by operation in the clinic of Harvey Cushing in 1926-27, where the author served as assistant resident physician. Of these tumors, 148 were removed wholly or partly during this time. A close check up has been made of the subsequent course of the patients operated. The following table printed from the Lancet indicates the immediate and late results of operation in the different types of brain tumor.

The table suggests the general impression that about half the brain tumors coming to operation are benign and half are malignant. Concerning himself with more than operative revival, the author has probed the value of treatment deeper by considering the period of useful life patients enjoy after removal of brain tumors. The different types of *glioma* have been found to vary greatly in malignancy. Thus, *glioblastoma multiforme*, a rapidly growing cerebral hemisphere tumor of middle aged or old people, occurred in 8 patients, and all died within a short

time after operation. A similar result was noted in 5 cases of *cerebellar medulloblastoma*, a glioma affecting children and young adults. Of 2 patients, however, with the same tumor type located in the cerebrum, 1 survived nearly 5 years. The *astroblastoma* shows a variable growth rate. One patient in 4 is alive at present, and another survived nearly 5 years. One of two cases of *oligodendroglioma* lived 9 years, having had 3 secondary operations. Although the majority of 15 patients with *cerebral astrocytoma* died within 3 years, 4 patients survived that period and 1 is still alive. The *cerebellar astrocytomas* furnish most of the survivals in the glioma group. This tumor of young adults and children is composed of mature astrocytes which accounts for its slow growth. Of the 4 patients operated, 3 have survived 9 years to the present. *Spongioblastoma polare* was encountered once, and the patient is still alive; *ependymoblastoma* once, the patient surviving 1 year.

Twenty-nine patients were operated for *pituitary adenoma*; 19 have survived the 7 to 9-year period. Of this number, 11 can do full work, and 4 can do no work. Many still have disturbances of reproductive function. Six of the 19 cases have had severe loss of vision.

*Meningioma*, a tumor of dural origin not infiltrating the brain, is thought to have the most favorable outcome. Of the 31 patients operated, 18 have survived the 7 to 9-year period. Eight patients are completely well; 6 can still work although they suffer major disturbances, such as visual loss, mental symptoms, and epilepsy, while the remaining 4 are unable to work because of severe cerebral symptoms.

*Acoustic neuromas* are morphologically benign, but occupy an unfortunate position at the base of the brain. The encouragement from the fact that 8 of

10 operated patients have survived the full follow-up period is dampened by the finding that only 2 can do full work. The remaining 6 complain of severe disturbances of balance.

The above comprise the majority of primary operable cerebral tumors. In this series of 157 cases, the chances of useful survival for the 7 to 9-year period are about 25 per cent. The disagreeable cerebral residua from operation should not deter attempts at complete restoration. This in many cases cannot be hoped for because the tumor has done its damage before removal. An idea of what technical perfection can do to improve the brain tumor patient's chances is to be had from the author's comparison of this series with that of Tooth, 1902 to 1911. The operative mortality has been reduced from 50 to 14 per cent., and the long term survival rate has increased from 16 to 40 per cent.

The manifold aspects of the cancer problem are overlooked many times by the physician. The complexity of the disease in the first place is such that its management is handled best by a group rather than by a single individual. To bring the patient with cancer into the hands of a group qualified by training and experience to treat the disease is the problem and obligation of society in general and the profession in particular.

Massachusetts recognized this fact in 1926 by the institution of a Cancer Program in the State Department of Health. This year H. D. Chadwick and H. L. Lombard (New England J. Med. 215:265 (Aug. 13) 1936), in commenting upon its progress, state that the death records of the State show the first decrease in cancer deaths of both sexes in the 20th century. The Plan includes 5 major activities: hospitalization, tumor diagnostic service, research, diagnostic clinics and education.

Those familiar with the difficulties in care of many advanced cancer patients in the general hospital will realize the necessity for a state cancer hospital such as Massachusetts has in Pondville. This hospital has facilities for diagnosis and treatment to adequately care for all patients eligible for admission, *i. e.*, those with or suspected of cancer. The staff is drawn largely from an adjacent medical center.

A tumor diagnostic service is maintained by the coöperation of the Health Department and the Harvard Cancer Commission. This service provides a 48-hour free diagnostic service on material sent in by any doctor or hospital in the State.

The research has been occupied so far with a statistical consideration of the etiologic factors in cancer from the clinical standpoint, and of the care and treatment of the cancer patients.

A centralization of many scattered tumor clinics has been urged whenever feasible. These clinics serve as diagnostic consultation clinics from which the patient is sent back to his referring doctor for treatment or recommendation. Educational literature published by the State advises the patients to see their physician. Physicians are urged to accompany their patients to the clinics in order to take part in the discussion. The fact of mutual satisfaction is evidenced by more patients reaching the doctor and thereby reaching the clinic through his recommendation and by the lessened tendency of the patients to waste valuable time by shopping about.

An educational program is carried out for the public. The radio and newspaper are utilized by committees formed in clinic cities to acquaint the people with the early signs of cancer, the danger of delay, and the benefit of proper treatment. Every physician in the State receives literature, including articles by

specialists, on the various types of cancer. This program keeps the physician in touch with the field, encouraging him as the pivotal figure in cancer control to teach the layman. Such coöperation between the physician and the State for the patient's benefit will do much to relegate the so-called trend toward "Socialization of Medicine," to its proper meaningless and superfluous position.

**Treatment.**—A cursory review of the literature on *tumors of the carotid body* reveals some 230 cases. The most recent group has been collected by E. W. Peterson and L. H. Meeker (Ann. Surg. 103:554 (Apr.) 1936), and includes 18 cases from members of the New York Surgical Society, some of which were cases observed by the author. About 90 per cent. of these tumors had a similar pathologic picture and were thought to represent paragangliomas. Nearly half of them were malignant pathologically, and 5 deaths resulted from tumor growth after operation. In this series there was no operative mortality.

The chief difficulty in surgical attack on these tumors is their intimacy with the common carotid artery. In tumors necessitating ligation of this vessel the incidence of postoperative paralysis from cerebral ischemia is high and the mortality in many clinics is 30 per cent. Many surgeons prefer to avoid removal of benign carotid tumors necessitating ligation because of their slow growth. In the group likely to be malignant, the authors have suggested a plan of attack to cut down the high operative mortality from common carotid ligation. It consists in systematic **preoperative compression of the common carotid** daily for weeks in order to establish collateral circulation; then **exploration** to attempt **removal** without carotid ligation. If ligation is necessary, biopsy is taken and temporary occlusion by ligature or

a Halstead band is accomplished with the idea of removal at the first sign of hemiplegia. If the biopsy shows **malignancy**, **palliative irradiation** may be adopted or a decision for a **radical secondary operation** may be entertained with considerably lessened fear of prohibitive cerebral complications.

The types of *malignant lymphomatous tumors of the tonsil* encountered in 37 patients by H. Jackson, Jr., F. Parker, Jr. and A. M. Brues (Am. J. M. Sc. 191:1 (Jan.) 1936) are as follows; reticulum cell sarcoma, 16; lymphocytoma, 13; Hodgkin's disease, 4; lymphosarcoma, 2; giant follicle lymphoma, 1; and plasmacytoma, 1. The tumor mass always occupied the tonsillar fossa, and was usually firm and rubbery. Ulceration was noted in only 5 instances.

The malignancy of these lymphatic tumors is evidenced by the fact that only 4 of 37 patients are alive 5 years after treatment. Further prognostic caution is advised, since 2 patients who survived 10 years after the onset, ultimately died of recurrence. In 67 per cent. metastases were already present when the patient was first seen. In the patients seen before metastases had developed, the average period until death intervened was 5.3 years, while in those seen after metastasis it was 1.7 years. The mitotic activity of the tumor gave some evidence of its growth tendency. One case developed acute lymphatic leukemia. The patient with the tonsillar plasmacytoma died 8 years later with multiple myeloma of bone.

In the cases seen some years ago 4 to 12 **gold radon seeds** of 1 mc. each were implanted into the tumor and an additional **radium** application was made over the affected lymph nodes. Recently seeds have been used in conjunction with **high voltage x-ray** (200 KV.) in doses of 600-800 r. The authors now advocate a dosage as heavy as employed

in the treatment of carcinoma of the tonsil. Many tumors were found to be highly radiosensitive; but recurrence in the neck, or in local or distant lymph nodes took place promptly. Rapid disappearance of the tumor was with some exceptions a good prognostic sign.

The incidence of *primary carcinoma of the lung* varies between 2 and 19 per cent. of all cancers. The revival of interest in cancers in this location has been fostered by the success of pneumonectomy as a technical procedure and its promise as a method of cure. E. A. Graham (Ann. Surg. 103:1 (Jan.) 1936), in an encouraging review of the treatment of primary cancer of the lung, states that there have been reported to date 9 successful **pneumonectomies** for *bronchiogenic cancer* and that no doubt many more will soon follow. In proven cases of carcinoma of the bronchus he can find no instances of x-ray being effective. Tumors of major bronchi give earlier symptoms, extend more slowly, and are more amenable to surgery than those in minor bronchi or at the lung periphery. Cartilage in the larger bronchi acts as an effective barrier to early spread. The author quotes figures from Tuttle and Womack showing that 23 cases of major bronchus carcinoma had an average duration of life of 26.3 months; while 21 cases of carcinoma of minor bronchus or of the lung periphery had an average duration of 7.3 months. The vascularity of the lungs accounts for widespread metastases, such as liver, kidney, adrenal and brain. With the promising results of pneumonectomy and the diagnostic efficiency of the bronchoscope, the physician should satisfy himself that a curable lung carcinoma is not confronting him in the patient past middle age with unexplained insidiously arising cough.

The place of **deep irradiation therapy** as an integral part of the manage-

*Comparison Between Cases of Bladder Cancer Receiving Operation Alone, and Those Receiving Operation and Irradiation*

| Years Postoperative | Per Cent. Alive After Operation | Per Cent. Alive After Irradiation and Operation |
|---------------------|---------------------------------|---|
| 1                   | 47                              | 77  |
| 2                   | 30                              | 58  |
| 3                   | 20                              | 42  |
| 4                   | 12                              | 31  |
| 5                   | 7                               | 23  |

Number of survivals expressed as percentage of each group.

ment of *bladder carcinoma* is shown clearly in the accompanying table from J. R. Andrews and C. A. W. Uhle. (Am. J. Cancer 26: 507 (Mar.) 1936). Their series includes 15 patients on whom varying surgical procedures alone had been carried out, and 27 patients receiving similar surgical treatment combined with external x-ray therapy.

The authors' plan, after *cystoscopy* and *biopsy*, for operable bladder cancer consists, of course, of **preoperative** and **postoperative external x-ray irradiation**.

Reliable and unprejudiced information on the rôle of **irradiation** therapy in *bone tumors* is to be found in a recent paper by O. N. Meland (Radiology 27: 410 (Oct.) 1936). His report includes personal therapeutic results of radiologic treatment of benign and malignant bone tumors.

Osteochondromas, giant cell tumors and bone cysts make up the benign group. Osteochondromas, show no response to irradiation. *Giant cell tumors* on the other hand, are often cured by **irradiation**. **Surgery** also claims many cures. For a quick result, the author admits that **surgery with cauteriza-**

**tion** is better. In irradiation, the object is to produce a slow sclerosis by repeated series of moderate intensity treatments. *Bone cysts* show little response to x-rays, but their *recurrence* after surgery may be *prevented* by **irradiation**. Among the malignant types of bone tumor the author considers chondrosarcoma, endothelial myeloma, osteogenic sarcoma, hemangioma, multiple myeloma, and metastatic carcinoma. In an occasional one of 8 cases of *chondrosarcoma*, **irradiation** seemed to slow the inevitable progress of the tumor and to relieve pain, but in the majority of cases x-rays were without effect.

*Endothelial myeloma* is the most radiosensitive of all bone tumors. The author's 7 cases, even 2 who passed the 5-year period only to succumb subsequently to the disease, exemplify the tendency of endothelial myeloma to recur and metastasize. In fact, A. Brunschwig has shown that radiosensitivity of Ewing's sarcoma is variable (*Ibid.* 27: 328 (Sept.) 1936). He reports 3 cases which were given 16,080 r, 5000 r, and 6320 r, respectively, over relatively short periods. Subsequent necropsy studies showed that proliferating masses of cells still persisted at the primary site. *Multiple myeloma* is very radiosensitive but its generalized nature precludes hope of permanent cure. *Hemangiomas* of bone are similar to endothelial myeloma in ready response but later recurrence and metastasis. *Osteogenic sarcomas* are as a class resistant to irradiation. In general, temporary regressions and equally temporary relief of pain are all that can be expected from **x-ray** therapy. Although the author indicates that there are cases of osteogenic sarcoma treated by irradiation alone reported alive after 5 years, he includes none in his series. Surgery, no doubt, is the method of choice. Massive **pre-operative x-ray** over the shaft of long



bones and over the tumor, as suggested by the author, may deserve a trial. Most metastatic tumors in bone are carcinomas. The thyroid, breast, prostate and kidney rank as foremost primary sites. Often startling relief of symptoms and return of a patient to a previously active status for many months are secured by **irradiation** of bones with advanced metastatic involvement. It is seldom too late to try for such a result.

The author has found that usually tumors not sensitive to lower voltages have not been further influenced by supervoltages. With the exception of Ewing's tumor, it is questioned whether prolonged heavy irradiation of bone tumors will result in any appreciable increase in curability. With such irradiation, two complications must be anticipated, *i. e.*, (1) radiation osteitis, and (2) epiphyseal atrophy in children.

The procedure frequently adopted by the author is delivery of the x-rays through 2 or 3 ports, using 200 KV., 4 ma. current, 50 cm. distance, 0.5 mm. Cu. and 1 mm. Al. filter for a total of 200-300 r per port per day. In giant cell tumors 600-800 r per port total is administered. After 3 months' rest a similar series may be repeated. In malignant bone tumors the filtration is increased to 1 mm. copper and the dosage is increased to a total of 1200-1600 r per port, treating the patient daily.

Three factors are responsible chiefly for the unsatisfactory and inconstant results in the treatment of *fibrosarcoma of the soft parts*. These are the apparent clinical benignity of the early tumors at the first examination; their uncertain subsequent behavior following operation; and the difficulty of prognosis from the microscopic slide. Certain aspects of these difficulties have been considered in an admirable review of 163 cases of fibrosarcoma of soft parts with adequate

clinical data by S. Warren and G. N. J. Sommer, Jr. (Arch. Surg. 33:425 (Sept.) 1936). The authors find nearly four-fifths of fibrosarcomas occurring between the ages of 30 and 70 years. Swelling, as in most benign tumors of soft parts, is the first sign of fibrosarcoma. The tumor is often movable and may simulate encapsulation so well that the surgeon frequently falls into the error of shelling it out. Thereupon recurrence promptly occurs. The tumor presents diagnostic difficulties to the pathologist also, as is indicated by the finding of slides listed under fibrosarcomas which were granulation tissue, local fibrosis and sclerosing hemangioma. **Wide and deep excision** of the primary tumor was found to be the most successful type of treatment. Inability to do this in the head and face has shown fibrosarcomas of this region to be of high malignancy. Radiotherapy was found devoid of curative value. The authors cite occasional cases where **radiotherapy** may have shown palliative value.

From the general class of *fibrosarcomas* the authors make only one subdivision; namely, *neurogenic fibrosarcoma*, of which they found 63 cases. No essential difference between the clinical behavior of the two types is noted. They point out that the important indication of high malignancy in these tumors is the presence of tumor giant cells. The 3-year follow-up percentages are as follows: fibrosarcoma 35 per cent. alive and well; neurogenic fibrosarcoma, 37 per cent.; fibrosarcoma with tumor giant cells, 8 per cent.; neurogenic fibrosarcoma with tumor giant cells, 36 per cent. The average total duration of these types from onset to death is fibrosarcoma, 7 years; neurogenic fibrosarcoma, 7.8 years; fibrosarcoma with tumor giant cells, 2.2 years; neurogenic fibrosarcoma with tumor giant cells, 5.5

years. Recurrence developed in over one-third of the cases. This usually took place in the first year after operation. Of 34 cases developing metastasis, all but six did so only after a recurrence. For this reason it is urgent to **remove** fibrosarcomas **widely and deeply**, with healthy margins of tissue on all sides; in tumors of an extremity, to **amputate** provided adequate excision is impossible, instead of waiting for recurrence and running the risk of metastasis in the interval or the development of an inoperable recurrence.

Although the procedure is not new, the **intraspinal injection of absolute alcohol** for the relief of intractable *pain* in malignant disease deserves mention. The relief afforded by this simple means, according to W. D. Abbott (Am. J. Surg. 31:351 (Feb.) 1936), is often as satisfying as that from formidable operations for cordotomy or neurolysis. The technic requires only experience in spinal puncture and is carried out as follows:

The patient is placed on the side opposite to the painful one. One c.c. (16 minims) of absolute alcohol is injected over a period of 4 to 5 minutes into the spinal canal at the desired level. The position is maintained for 15 minutes and the patient's head is kept low for 2 hours. After a period of 24 hours' confinement to bed, the patient is allowed up and about. If the pain is bilateral, the injection is repeated in 5 days, with the patient lying on the opposite side; or on the same side as previously, if relief is not obtained.

In this series 25 patients were injected 40 times for various ailments, including carcinoma. Complete relief was secured for 21 patients, partial relief for 2, and no relief for 2 cases. One moribund patient with carcinomatosis died the day following the injection. Injections were carried as high as the first dorsal interspace. Two patients developed temporary leg paresis, but bowel and bladder function was not disturbed.

In 1889, Schinzinger recommended **oöphorectomy** in menstruating women with *breast cancer*. In the 10 years that followed, many utilized this suggestion, but the results seemed inconclusive. The ease and safety of **sterilization by irradiation** has brought about renewed attempts to delay metastasis in breast cancer. D. Quick (J. A. M. A. 101:2091 (Dec. 30) 1933) has found x-ray castration of women with breast cancer to exert little influence on the course of the disease.

Of the few groups recently available for study, R. Dresser, however, (Am. J. Roentgenol. 35:384 (Mar.) 1936) has reported a series which includes 59 women with bone metastasis from *breast cancer* who were sterilized by x-ray. Of the series, 30 were women under 45, and 29 were past menopausal age. In the former series, 9 cases showed an actual regression of the bone tumors and a concomitant relief from pain; 13 showed relief of pain but no metastatic regression; and 8 showed no response to treatment. In the group past menopause, nearly half enjoyed some relief from pain, but none evidenced tumor regression. Considering the poor chances of menstruating women, particularly those who become pregnant, the author is trying x-ray **sterilization following radical excision** for operable breast cancer. No results of this régime are available yet, but there is hope of raising the 3-year-cure rate of 15 per cent. reported by Lee in 191 cases of breast cancer in women under 40 years of age.

A. A. Strauss, S. F. Strauss, R. A. Crawford and H. A. Strauss report a series of *carcinomas of the rectum* treated by **surgical diathermy**. Coagulation of low rectal carcinomas is accomplished by an insulated electrode introduced through a glass cylinder. Multiple treatments are advised in some cases. Forty-two patients were treated with

surgical diathermy, 20 requiring a **primary colostomy**. Eleven patients died within 3 years, 2 as a direct result of perirectal sepsis induced by diathermy. The remaining 31 patients are in good health, 10 after 5 years, 9 after 4 years, and 12 after 3 years or less.

Secondary in remarkability only to the high rate of cure is the fact that 22 patients still have the full use of the rectum. Such results are worthy of some efforts at confirmation.

J. M. Lynch and G. J. Hamilton (Am. J. Surg. 32:435 (June) 1936) present

5 cases of 5-year cures by **radical resection** for *carcinoma of the rectum* which were classed previously as inoperable. The operability of these lesions can be established frequently by trial only. The dubious curative power of radium and x-ray for cancer in this site should throw the balance in favor of operation, if only the remotest chance of cure or relief exists. Procrastination, pessimism about permanent colostomy, and resort to less hopeful methods of treatment still are keeping some patients from their chance of cure.

## SURGERY OF SYMPATHETIC NERVOUS SYSTEM

By PAUL G. FLOTHOW, M.D.

**TECHNIC.—Lumbar Gangliectomy.**—Flothow has set forth a refinement in technic of the operative approach to the lumbar sympathetic ganglia by an extraperitoneal route instead of the transabdominal approach.

The operation is done through a transverse incision at the level of the umbilicus from the edge of the rectus muscle laterally into the flank. The fibers of the external oblique, internal oblique, and transversalis muscle are split in turn, and from this point the operation is exactly the same as in his former technic. After the sympathetic chain is removed, the muscles come together and require only a few sutures for closure. The same advantages are obtained as those peculiar to the McBurney incision, *viz.*, lessened hospital stay and insurance against hernia.

**Cervicodorsal Gangliectomy.**—The anterior approach to the cervicodorsal ganglia is Royle's operation and has been described by Flothow.

The operation is performed through an incision above and parallel to the clavicle, extending from about 1 inch lateral to the midline, 1 finger's breadth above the clavicle for a distance of about 3 inches. The clavicular head of the sternomastoid muscle is then severed and the cervical fascia dissected. The anterior scalenus muscle is cleared, care being taken not to injure the phrenic nerve which is

retracted medially. The anterior scalenus is severed just above its attachment to the first rib, exposing the subclavian artery and the pleura. The subclavian artery is cleared, and, when necessary, the thyroid axis is ligated. The artery is then retracted downward and medially, exposing the dome of the pleura, which is freed by blunt dissection from its attachment to the first rib, care being taken not to rupture the pleura. The pleura is then retracted downward and medially. The sympathetic trunk may be identified by palpation, as it crosses over the neck of the first rib at its attachment with the vertebra. It is a comparatively simple matter to pick up the trunk and to clear the entire stellate or inferior cervical ganglion and sever all of its rami well above its upper limits. The dissection is then carried downward and backward into the thorax and it is not difficult to get well below the third dorsal ganglion.

It is possible to carry the dissection further and remove as low as the fifth dorsal ganglion. At times, very troublesome veins and arteries are encountered in close association with the sympathetic trunk and ganglia. These vessels may be very annoying and interfere with the operation to the extent that the procedure is considerably prolonged. As a rule, however, it can be accomplished in less than an hour. After the operation is completed, closure is rapid and simple. A few sutures are taken in the deep cervical fascia and the sternomastoid muscle is approximated. It is rarely necessary to drain. The postoperative course is unevent-

ful and these patients are allowed up on the second or third day after operation. Both sides may be done at one sitting. It is preferable and safer to do it at two operations with a 3- to 5-day interval.

**Injections.**—The following technic has been reported for diagnostic injections of the superior hypogastric plexus by P. G. Flothow:

Needles are inserted 7 cm. from the midline just above the crest of the ilium inward at an angle of 45° from the surface until the body of the fifth lumbar vertebra is encountered. The needle is then advanced over the anterolateral border of the body of the vertebra for a distance of 1½ to 2 cm. on each side. Ten c.c. (2½ drams) of 1 per cent. **procaine** are then deposited in each needle, thus effectively blocking the superior hypogastric plexus. This injection is of great importance in the treatment of *pelvic pain* and *dysmenorrhea*.

**THERAPEUTIC APPLICATION.**—**Multiple Sclerosis.**—The heretofore utterly hopeless disease of multiple sclerosis has been taken out of that category if the reports of N. D. Royle, F. S. Wetherell and P. G. Flothow (Northwest Med. 35:410 (Nov.) 1936) may be believed. Royle reports 4 cases successfully treated by sympathectomy; Wetherell reports 8 cases; and Flothow reports 18. If it is true that sympathectomy is advantageous in this disease, it will be necessary to revise the present concepts of its pathology to some extent.

Wetherell feels that the sclerosis which occurs in the brain and spinal cord is due to the lack of blood supply in these organs, and that sympathectomy gives its beneficial effects by reason of increasing the blood supply to the brain and spinal cord. This theory is easily tenable if the history of these cases is taken into consideration. One of the most characteristic features of the disease is the occurrence of remissions, during which the patient will experience a marked improvement in his condition. If it is assumed that the various symp-

toms of the disease appear only when death of tissue occurs in the brain and spinal cord, then there is no explanation for the occurrence of remissions. They may be easily explained on the basis of a temporary improvement in blood supply which renders a portion of the cord or brain which has not been functioning, due to lack of blood supply, into a functioning portion for the time being. In other words, it is felt that the pathology of the disease may be a sclerotic area, which is, of course, functionless, surrounded by a zone of tissue in which the cells are viable but are not functioning due to insufficient blood supply. As time goes on, the sclerotic area increases in size and the viable but functionless zone also radiates and increases in size. It is this functionless but viable zone, which, it is felt, can be saved by increasing the blood supply through removal of the necessary sympathetic ganglia. It is believed that by this operation it will be possible not only to save the danger zone of tissue and thus cause a marked improvement or a permanent remission in the course of the disease, but also to prevent its progression.

Flothow reports a series of 18 cases treated by **cervicodorsal sympathectomy**. His results have not nearly approached those reported by Royle and Wetherell. He states that surgical treatment should be recommended only in carefully selected cases and the earlier in the course of the disease the treatment is applied, the better will be the results. In advanced cases that have lost the ability to perform purposeful movements and to walk, little can be hoped for other than possibly an interruption in the progression of the disease. His results have been much better in men than in women. He reports improvement in 75 per cent. of male cases and in only 40 per cent. of the females. One very interesting case is recorded of a

woman upon whom lumbar sympathectomy was done in 1933 for pain and spasticity of one leg, due to multiple sclerosis. She was completely relieved until 1936, when she developed symptoms referable to involvement of the brain stem and the optic tracts. Her vision was rapidly diminishing and in a period of a few months' time the visual fields became markedly contracted, so that she had practically only central vision. Following bilateral cervicodorsal sympathectomy the visual fields rapidly returned to normal and all of her symptoms of vertigo and inability to use the arms properly were markedly improved.

It would seem from his report that while sympathectomy in the treatment of multiple sclerosis is far from a cure, and while the results are not nearly as good as might be expected from previous reports, this form of treatment has some merit and is worthy of consideration in cases in which all other forms of therapy fail.

**Essential Hypertension.**—Perhaps the most interesting and the most important work of the past two years has been the application of sympathetic surgery to the treatment of essential hypertension. Brown, Craig and Adson, M. M. Peet, and others report favorable results in the treatment of essential hypertension by surgery of the visceral nerves.

The Rochester group have been pioneers in this method of treatment, although Danielopolu first conceived the idea of resection of the splanchnic nerves for the treatment of hypertension in 1923. This was applied by Pieri in 1930. His approach to the splanchnic nerves was by a supradiaphragmatic route. Adson and Craig originally resected only the splanchnic nerves. The results of this operation were not satisfactory, although the patients were clinically improved. Adson and Craig then advocated

bilateral intradural section of the anterior spinal roots from the sixth dorsal to the second lumbar inclusive. This is an operation of considerable magnitude, requiring a very long laminectomy, and for that reason attempts have been made to produce the same results by an operation of less magnitude. A. W. Adson (West. J. Surg. 44:619 (Nov.) 1936) now recommends subdiaphragmatic section of the splanchnic nerves, removal of the upper two lumbar sympathetic ganglia and resection of a portion of the adrenal gland bilaterally. He feels that the results are equally as good as those following the intradural operation. The REVIEWER uses the same technic, but adds to it the removal of the celiac ganglion on each side, and does not resect a portion of the adrenal gland. He feels that the results following this more complete denervation should be even better. (From his experience on the human and dissections on the cadaver the REVIEWER feels that it would be possible to remove both celiac ganglia at one operation from the left side. By this method, both sets of splanchnic nerves would be severed, both celiac ganglia removed, and the left first and second lumbar ganglia also, which he feels would be just as successful as the complete bilateral operation described above. In his last case, after the entire left celiac ganglion had been exposed preparatory to removal, the right ganglion prepared in the field and could easily have been removed. On the cadaver the two ganglia lie very close together, being connected by a stout band of nerve fibers.)

**SELECTION OF CASES.**—Undoubtedly cases in which the hypertension is due to arteriosclerosis should be excluded, and this type of treatment be reserved for true cases of essential hypertension, the exact etiology of which is not known.

These cases undoubtedly have a tremendous element of vasopressor activity, which is probably primarily due to hormonal endocrine disturbances. The most favorable cases are the younger individuals, preferably under 40 years of age, with a history of short duration and slow progression. After cardiac and kidney damage appear, or edema of the optic discs and retinal changes, the risk is tremendously increased and the results much less favorable, although in the REVIEWER's experience one case of this type has shown a marked improvement.

A simple *diagnostic test* is that known as the *cold test*, in which the patient's hand is immersed in ice water at 4° C. (39.2° F.). Within 30 seconds a marked rise in blood-pressure appears, which indicates the severity of the vasomotor response of the individual case. Normal individuals rise very little, usually not over 10 points, whereas the essential hypertension patient may show a rise of 50 or even up to 100 points. In some cases where the normal level of blood-pressure is very high and one hesitates to give these people a sudden increased pressure for fear of a vascular disaster, a reverse test may be used as suggested by Lundy, *viz.*, the intravenous injection of **pentothal**, which causes a lowering of the blood-pressure to what is apparently the basic level. In one case the pressure dropped from 270 to 140 within 1 minute. The REVIEWER has also successfully injected the **celiac ganglia** and produced a marked fall in blood-pressure. This procedure has also been used in the REVIEWER's clinic as a diagnostic test.

**SURGICAL TECHNIC.**—A. W. Adson, W. M. Craig and G. E. Brown (Surg. Gynec. and Obst. 62:314 (Feb.) 1936) use the following technic:

The incision and position of the patient are similar to those used for exploration of the

kidney. The line of incision is like a hockey stick with the staff portion placed just lateral to the rectus spinous muscles and the club portion extending downward and forward over Pettit's triangle just above the crest of the ilium. At the upper portion of the wound the oblique fibers of the latissimus dorsi are incised, exposing the twelfth rib. The incision is extended downward and the common aponeurosis of the external and internal oblique muscles and the transversalis muscle where it fuses with the lumbar fascia is incised until it extends into Pettit's triangle. Subperiosteal resection of the twelfth rib is then carried out, being very careful not to injure the pleura. The finger is then introduced into the subdiaphragmatic space and the subcostal ligament of the twelfth rib is incised to allow upward retraction, which gives a better exposure. Using an illuminated retractor, a retroperitoneal dissection is made, displacing the liver and the abdominal contents forward and downward. The crus of the diaphragm is then found and the splanchnic nerves are exposed. These are resected and the first and second lumbar ganglia below are also resected. Adson then incises the perinephritic fat to expose the suprarenal gland and removes a portion of it. Other workers do not do this part of the operation and the author adds to it complete resection of the celiac ganglia. Closure is made along anatomical lines.

**RESULTS.**—Excellent results have been reported in selected cases by various authors. While it is still too early to state anything in regard to the permanent value of this treatment, it seems to be a step in the right direction, and as long as medical methods offer as little as they do, this type of surgery gives considerable hope for the future of the treatment of essential hypertension.

#### ***Pelvic Pain and Dysmenorrhea.***—

The literature continues to show favorable results in the treatment of pelvic pain and dysmenorrhea by **resection of the superior hypogastric plexus**. A common mistake is made in the course of this operation in that the dissection and resection is made too low. The resection should be carried from well over the bifurcation of the aorta downward

for a distance of 2 inches and laterally to the iliac arteries. While it is not necessary, stripping the iliac vessels in the same field probably adds to the denervation. This technic has been frequently described, namely, by Herrman and Fontaine, Wetherell, De Courcy, Adson and Masson, Flothow and others. The most satisfactory results are obtained in cases of functional dysmenorrhea which are not associated with pelvic pathology. Flothow advises a diagnostic injection during the period of pain, and makes the following statement:

"The majority of cases of pelvic pain which do not respond to ordinary gynecological treatments may be relieved by an interruption of the fibers coursing through the superior hypogastric plexus. Diagnostic injection of the pelvic sympathetic nerves should precede any surgical undertaking directed toward the relief of pain by denervation of the superior hypogastric plexus. Cases of functional dysmenorrhea are particularly amenable to this treatment."

**Migraine.**—Ligation of the middle meningeal artery has been suggested for the relief of migraine. It seems possible that this might relieve the pain in some cases, but the associated symptoms of nausea and visual disturbances which could be caused only by cerebral involvement should not be relieved by this procedure. The procedure of choice would, therefore, be **resection of the cervicodorsal sympathetics**. Successful cases have been reported by Dandy, Craig, Flothow and others. Flothow emphasizes the importance of *diagnostic injections* during a period of pain, to determine whether or not sympathectomy is indicated. He cautions, however, to be on guard for psychic effects, as these people are very susceptible to suggestion and a positive result following injection may be followed by an

operative failure to relieve pain. He further states that allergic conditions and all other methods of treatment such as the use of Gynergin, Chondroitin and other drugs should be used before advising surgery.

**Sympathectomy in Raynaud's Disease.**—It has long been evident that the results of cervicodorsal sympathectomy have not been nearly as satisfactory in the treatment of Raynaud's disease as those following the lumbar operation. Various opinions have been set forth as to why this should be true. Many have felt that it was due to incomplete denervation; others, that it was due to regeneration of sympathetic fibers, and still others, that it was due to some difference in the physiology of the blood vessels of the hand as compared with the foot. H. H. Woollard (Brit. J. Surg. 23:425 (Oct.) 1935) states that the normal central vasomotor tone of the blood vessels of the feet is much in excess of that of the blood vessels of the hands because of the necessity imposed upon these vessels by the upright position. He considers that this is the reason why sympathectomy and its consequent removal from central control of vasomotor action is more effective in the feet than in the hands where central vasomotor impulses are much less than they are in the feet.

In the last few years some very interesting experimental work has been reported by Smithwick, Freeman and White, and others, showing that dorsal sympathectomy with removal of the inferior cervical and first 2 or 3 dorsal ganglia renders the blood vessels of the upper extremity much more sensitive to the effects of adrenalin circulating in the blood. They have shown that amounts of adrenalin which in the completely sympathectomized extremity cause marked vasospasm, have no such effects upon the normally enervated ex-

tremity. They infer from this work that for some reason the smooth muscle of the blood vessels in the extremity has been rendered more sensitive to adrenalin by sympathectomy. In a search for an explanation of this phenomenon and why the arm should differ from the leg in its results, they have concluded that it is due to a difference in the type of surgical denervation in the two locations. Lumbar sympathectomy with removal of the second, third and fourth lumbar ganglia is almost entirely preganglionic as far as the fibers to the lower extremity are concerned, whereas cervicodorsal sympathectomy, as now usually practiced, is largely postganglionic to the blood vessels of the upper extremity. Feeling that the difference in the results is due to a difference in physiology based upon the level of the attack, R. H. Smithwick (*Ann. Surg.* 104:339 (Sept.) 1936) and E. D. Telford (*Brit. J. Surg.* 23:448 (Oct.) 1935) have devised operations which they feel are almost entirely preganglionic for the upper extremities. White claims that although at the present time it is too early to be certain, cases operated by this method have shown results equally as good as those in the lower extremity. Telford

exposes the inferior cervical first, second and third dorsal ganglia through the anterior approach. He does not disturb the inferior cervical nor the first thoracic ganglia, which are frequently fused, but severs the white rami to the second and third dorsal ganglia, and severs the trunk below the third ganglion.

**TECHNIC OF SMITHWICK OPERATION.**—An incision is made  $1\frac{1}{2}$  inches from the midline about 3 inches long, centering opposite the second dorsal spine. This is carried down through the muscles to expose the third rib; which is removed with its transverse process for a distance of 1 inch. The inner  $1\frac{1}{2}$  inches of the second and third intercostal nerves are resected and the dissection of these nerves is carried into the intervertebral foramina, in order to sever both anterior and posterior roots, and thus avoid missing any centrally-placed white rami. The sympathetic trunk is severed below the third dorsal ganglion and the proximal end is sutured into the muscle, in order to avoid any possibility of regeneration. He states that since this technic has been used, the results are equally as good as those reported in the lower extremities.

It is to be hoped that time will prove this type of procedure to be just as effective in the treatment of Raynaud's disease in the upper extremities as lumbar sympathectomy has proved successful in the lower extremities.

## UROLOGY

By ELMER HESS, M.D.

**ANESTHESIA.**—The selection of an anesthetic to fit the peculiar needs of the urological patient must be emphasized. Due often to the exceptionally poor general condition of many of these patients, more and more care and selectivity must be exercised if the best surgical results are to be attained.

In 1934, the REVIEWER published his results with epidural injections of **novocaine** and classified the cases where this procedure seemed applicable. These ex-

periences have been verified further by 3 observers during the past year.

F. L. Senger and J. J. Bottone (*J. Urol.* 36:71 (July) 1936) draw these conclusions after trying this form of anesthesia in 45 cases. They believe there are many advantages and few disadvantages in properly selected cases, and have done every type of urological procedure under it. They believe it to be the safest anesthesia and have observed no effects on the heart and circu-



lation, respiratory system, gastrointestinal tract or renal parenchyma. The administration is very simple if the technic as described by the REVIEWER (E. Hess: *Ibid.* 31:621 (May) 1934) is followed.

L. Caporale (*Ibid.* 35:403 (Mar.) 1936) adds to the **novocaine** or **per-caine**, 5 c.c. ( $1\frac{1}{4}$  drams) of freshly prepared adrenalin and feels that the effects are more lasting and the anesthesia is more complete.

*Transurethral surgery*, having opened up the operative field in many elderly men who heretofore have been considered inoperable because of their general condition, has also for this same reason demanded the use of anesthesia under which the operative work may be done with complete anesthetic results without enhancing the operative risk. General anesthesia is obviously not to be considered in most of these cases and caudal block has some very definite disadvantages. To offset this, R. M. Nesbit (*Ibid.* 35:557 (May) 1936) says that **low spinal anesthesia**, controlled by keeping the patient upright during, as well as following, its administration, shows to advantage in confining the area of anesthesia to the operative site, and in over 95 per cent. of the cases maintaining normal circulatory and respiratory physiology. **Nitrous oxide** and **oxygen analgesia** is advantageously used in relieving apprehension in the nervous, but has no demonstrable effect on the blood-pressure level.

**Pentothal sodium** (a barbiturate) is another substance that can be used intravenously. R. M. Tovell and G. J. Thompson (*Ibid.* 36:81 (July) 1936) have demonstrated that almost any type of instrumentation can be accomplished following the induction of anesthesia by means of the intravenous administration of pentothal sodium. Forty-two patients were subjected to *transurethral prosta-*

*tectomy* under its influence. The cystoscopic manipulation of *ureteral calculi* and many other operative procedures are possible. It is best suited to cases where the operative manipulation can be completed in 30 minutes. In cases when, because of some idiosyncrasy or length of operative procedure, anesthetic effects are insufficient, supplementary inhalation anesthesia may be used.

**BLADDER.—CALCULI.**—In discussing calculus in the bladder (H. Lett (Brit. J. Urol. 8:205 (Sept.) 1936) remarks that the treatment in the hands of the expert may best be carried out by lithotrity, but that in the vast majority of cases, **simple suprapubic cystostomy** with removal of the calculus is easier and far more satisfactory.

**TUMORS.**—Hemorrhage from the urinary bladder calls for immediate cystoscopy following the first hemorrhage. It almost invariably means tumor and unless immediately investigated, the condition may go on in a very short time to the point where, if diagnosed, treatment may be of no avail.

Urinary hemorrhage as a symptom and not a disease is discussed by E. Hess (Pennsylvania M. J. 39:698 (June) 1936) with the following conclusions:

1. Bleeding from any part of the urinary tract calls for immediate complete urologic survey.
2. Uroscopy is of no definite value as a diagnostic process.
3. Sudden, painless, massive hematuria with or without recurrence, in the vast majority of cases, means tumor in the urinary bladder. Occasionally, it is indicative of ureteral or renal tumor.
4. Essential hematuria as a diagnosis should be dropped from the nomenclature.

5. Treatment:

- (a) The vast majority of bladder tumors may be treated through the

cystoscope by **fulguration** and the implantation of **radium**. This should be the method of choice.

(b) **Fulguration, radiation, and deep x-ray therapy.**

(c) **Suprapubic operation**, because of location, with **fulguration, radium, and deep x-ray therapy**. Very few bladder tumors will require this method of treatment; it should not be used routinely.

(d) In *inoperable carcinomas*, **deep x-ray therapy** followed by **fulguration and radium**, if possible.

(e) **Transplantation of the ureters with total cystectomy** may be tried in certain carefully selected cases if all other methods of treatment seem to be contraindicated. The indication for this procedure is very seldom seen and is followed by a very high mortality and a very high morbidity.

The Tumor Committee of the American Urological Association under the Chairmanship of R. S. Ferguson, and composed of H. L. Kretschmer, E. L. Keyes, B. S. Barringer, W. F. Braasch, A. L. Dean, Jr., A. J. Scholl, and Major R. O. Dart (J. Urol. 35:481 (Apr.) 1936), report on a study of 5-year end-results in 658 epithelial tumors of the bladder in the Carcinoma Registry of the Association, and although the Committee refrains from drawing conclusions from the data assembled, they have set forth certain factual results worthy of study. Of the 1354 epithelial tumors of the bladder now in the Registry, 658 were operated upon more than 5 years ago.

It is interesting to note that the size of the tumor is a decided factor in the end-result. Tumors less than 2 cm. in diameter were controlled 5 years in 30.3 per cent. of the cases, but when the tumor was more extensive than 5 cm. only 15.8 per cent. of such cases were

alive at the end of 5 years. The operative mortality among 468 patients subjected to open methods of treatment was 29 cases, or 6.2 per cent.

Total cystectomy was done in 2 cases; resection in 27; excision in 105; radium in 147; fulguration by open operation in 121; and the actual cautery by open operation in 66. Treated by the cystoscope: radium 54; fulguration 76; deep x-ray therapy 15. Thirty-five cases were not treated and the treatment was not stated in ten.

**CYSTOMETRY.—Bladder Dysfunction.**—During the past few years bladder dysfunction has been studied by a great many investigators. The diagnosis of the *neurogenic bladder* by means of the cystometer has been developed by several investigators. The use of the cystometer has placed the differential diagnosis entirely in the scientific class.

M. Muschat (Pennsylvania M. J. 39:493 (Apr. 1936) considers that there are two varieties of neurogenic bladder—the *hypertonic* and the *hypotonic*. The hypertonic bladder is small because of the increased muscle tonus and relaxed sphincter, causing true incontinence. The hypotonic bladder is just the opposite. It is large because of the relaxed musculature and spastic sphincter, the overflow of retention simulating incontinence. There are two points in the diagnosis of the neurogenic bladder that can be obtained cystoscopically. In the hypertonic bladder there is a relaxed sphincter wall and in the hypotonic bladder there is a very fine trabeculation of the bladder wall. However, this method of diagnosis is really only possible in well-advanced disease. To determine such a changed tonus, a cystometer is necessary. It is an apparatus designed to record the response or tonus of the detrusor to a gradual filling of the bladder

with water. The bladder pressure during the process of filling is observed and plotted on a chart. A pressure curve is thus obtained which reveals the actual behavior and response of the detrusor. The cystometer is simple in construction and operation. Such a study consists of passing a catheter into the bladder, connecting it with the cystometer, gradually filling the bladder with water and noting the changing pressures. A very important factor in this study is the determination of the point of the first desire to void. The patient should be instructed to state the slightest urge to urinate. After the bladder is filled to capacity, the patient is instructed to force it out against the manometer, thus recording another important factor—the maximal voluntary bladder pressure. Three factors are thus obtained: (a) first desire to void; (b) the pressure curve; and (c) maximal voluntary pressure.

The *normal curve* rises slowly with each 100 c.c. of filling, becoming more acute after 500 c.c. have been introduced. The normal first desire to void is between 150 and 250 c.c. The maximal voluntary pressure is between 40 and 60 mm.

The *hypotonic curve* is entirely different. It is flat. Instead of a gradual increase, the bladder pressure remains low and continues to remain low even after 500 c.c. of filling. The initial low pressure may remain unchanged in extreme cases even after 1000 c.c. of water have entered the bladder. The first desire to void is greatly delayed, appearing at 350, 500, or 800 c.c. of filling. The maximal voluntary pressure is low, always under 40 mm.

The hypotonic bladder, therefore, is the one with a low curve, shift of the first desire to the right, and low maximal voluntary pressure.

The *hypertonic curve* has just the opposite character. It is more acute than normal. The pressure rises rapidly after each 50 to 100 c.c. of filling. The first desire occurs at 50 or 100 c.c., the maximal pressure being extremely high, over 60 mm.

The hypertonic bladder, therefore, is the one with an acute curve, shift of the first desire to the left, and very high maximal voluntary pressure.

The definite alteration of at least two factors in the observation is obligatory evidence of a neurogenic bladder.

There are some pathological states which simulate the hypertonic or hypotonic bladder, such as acute and subacute cystitis, stone in the bladder and tumor, and which may give an acute hypertonic curve; a cystocele, diverticulum, renal reflux, and postoperative or postpartum dysfunctions simulate a flat hypotonic curve.

These possibilities may be eliminated by a proper urological examination, which should always follow every cystometric study. The possibility of a psychic factor altering the true picture of a cystometric study has been considered. Such a subjective psychic factor has no effect on the ultimate diagnosis. The three factors obtained in a cystometric study are so complete and interdependent in the normal that the change of one factor must bring about an alteration of the other.

There are some *nervous system lesions* that have a direct effect upon the urinary bladder. Of course, the first control is in the brain, and there is indubitable evidence that the highest centers for the management of micturition and movements of the external genitalia is in the paracentral lobule. F. Kennedy and S. B. Wortis (J. Urol. 36:255 (Sept.) 1936) observed a soldier with a single uncomplicated gunshot wound through his right frontal lobe whose

only difficulty was inability to hold his water. It is not unusual to find this sign in advanced arteriosclerotic cortical degeneration in the aged, in patients with right frontal tumors, or in children with cortical damage resulting from severe hydrocephalus.

*Voluntary micturition* is accomplished by impulses acting over the sympathetic pathways to cause contraction of the vesical trigone which opens the vesical orifice and over the parasympathetic pathways to cause contraction of the detrusor muscles.

Brain lesions are of the kind just described, or there may be urinary retention, which is the result of severe bilateral pyramidal tract lesions due to tumor or vascular disease of the brain.

The spinal cord reflex centers are often impaired by *spina bifida occulta* with resultant enuresis. *Spinal cord lesions*: both those above the sacral spinal cord reflex level and those of the lumbosacral cord have their effects. Complete transverse lesion of the spinal cord at any level causes the bladder to behave like an elastic reservoir with no activity. Reflex activity and muscular tone may slowly return. Incomplete lesions of the spinal cord may injure the inhibitory fibers or those concerned with voluntary micturition. This is the case in patients with *multiple sclerosis*. In cases of *tumor* or *myelitis*, urinary retention develops because of the uninhibited action of the sympathetic, while it is diagnostically characteristic of cervical syringomyelia to have little or no associated bladder disturbance.

*Lesions of the cauda equina* cause disturbances in the genitourinary tract. There may be disturbed sensation around the genitalia and anus. *Bladder and genital pain* sensations are usually carried from the bladder through the presacral nerve and **presacral neurectomy** has proven valuable in relieving

many patients, not only of pain but of some of their urinary difficulties following certain types of cord lesions. When this operation has been performed in men, it results in inability of the seminal vesicles and prostatic ducts to expel their secretion during coitus, although the psychic orgasm is retained. This operation may be of value in patients afflicted with marked *dysmenorrhea*. **Cordotomy** still affords the surest relief from otherwise *incurable bladder pain*.

F. C. Grant (J. Urol. 36:261 (Sept.) 1936) discusses the operation of **presacral ganglionectomy** in the treatment of some of these *cord bladder* cases. Mr. R. O. Ward, of London, emphasizes the value both of **cordotomy** and **presacral neurectomy** in many of these *neurogenic bladders*. Beer, of New York, emphasizes the fact that cordotomy is not indicated in Hunner's disease, or in other conditions in which presacral section could be used to relieve vesical pain. The chief value of the operation is to control the motor mechanism and conditions which relate to spasm of the sphincter muscles, but he emphasizes the fact that in many cases these **hypertonicities of the bladder neck** do not require presacral nerve section, as they can be almost completely relieved by simple **electrosection of the bladder neck**.

**GONORRHEA**.—Much has been written on the subject of the gonococcic infections, the cure of which still is one of the most difficult problems in modern therapeutics. During the past few years **hyperpyrexia**, or **fever therapy**, has been tried with varying results.

It is very interesting to note the observations of A. U. Desjardins, L. G. Stuhler and W. C. Popp (J. A. M. A. 106:690 (Feb. 29) 1936) in reporting cases of *gonococcic arthritis*. This dis-

ease in a large proportion of cases shows rapid subsidence as a result of **fever therapy**. Usually, the pain abates rapidly during the first treatment and in the very acute articular inflammatory cases the effect of fever therapy is spectacular. In virtually all the cases thorough treatment is followed by complete and permanent resolution of the inflammatory process. When it is chronic, the clinical manifestations abate rapidly and the infection is cured. It must be remembered, however, that when the infection has injured the bones, has already induced reparative changes in the form of connective tissue proliferation or deposition of bone, these as well as the resulting disturbances of function may be favorably influenced but the prognosis of complete return to function must be guarded.

Attention was called to the value of this form of treatment in those cases where, during febrile infections, a concurrent gonococcic infection became markedly improved. Several observers noticed that after acute attacks of scarlet fever, this phenomenon occurred. A great deal of work was done by Boerner and Santos. Culver described a case of *gonorrheal urethritis* that recovered after a 4-day attack of malaria. As far back as 1900, Wertheim claimed that the gonococcus grew well at 40° C. and could even tolerate 42° C., although this claim has not been substantiated by other investigators. L. G. Stuhler and W. C. Popp (Urol. and Cutan. Rev. 40:639 (Sept.) 1936) report a series of cases in which they used temperatures between 106° and 107° F. (41.1° and 41.6° C.) every 5 or 6 days. This method of treatment proved unsatisfactory because of the large number of sessions that were required to cure the infection. In order to avoid an undue number of sessions of treatment, they evolved the following technic: Treat-

ments were given every third day unless contraindicated by the patient's general condition. The first treatment is considered a trial session, the temperature being maintained between 105° and 106° F. (40.5° and 41.1° C.) for 5 hours. If no untoward results appeared, the second session lasted 6 hours, with a maintained temperature of 106° to 107° F. (41.1° to 41.6° C.). If the gonococcus is found to be present after the second treatment, the future sessions are all extended 2 hours at a temperature of 106° to 107° F. (41.1° to 41.6° C.) until smears and cultures are negative, and then 2 additional treatments lasting 6 hours each were given.

With 125 patients, 25 did not receive the complete course, either because they did not return after the first treatment or because they were not physically able to carry on and were advised to discontinue the treatment. The remaining 100 patients included 68 men and 32 women. They were divided into 2 groups: (1) those with an uncomplicated urinary infection and (2) those with some form of complication such as arthritis, prostatitis, urethral sinus, periurethral abscess, seminal vesiculitis, epididymitis, pelvic inflammatory disease, bartholinitis, prostatic abscess, ureteritis, pyelitis, or cystitis. The average duration prior to treatment was 3 months. In this group 92 per cent. were cured and 8 per cent. improved. The average number of treatments given each patient were six. The least number of sessions given any patient was one and the largest number twelve. No patient has been considered as cured until at least 3 consecutive negative reports were obtained. It was noted that during a course of fever therapy for gonococcic infection there seldom were any complications seen if they did not already exist.

These observations are extremely interesting and to a great extent have been verified by the work of other observers. J. K. Ormond (J. Urol. 35:551 (May) 1936) reports the treatment of 21 cases of *acute gonorrheal urethritis*; although the series is small and definite conclusions are not warranted, it still is large enough to show the good results that may be obtained. The treatment shows a very distinct favorable influence on the disease. In nearly every case a prompt and striking decrease in the disease was noted and the course of the disease seemed very much shorter. Very favorable effects were noted in the treatment of complications. Arthritis and epididymitis yielded promptly, and in one case of ophthalmitis, the condition cleared up after one treatment. It is interesting to note that the older or more chronic lesions seem to respond more promptly and more completely than did the recent or more acute lesions. Of course, this may be due to the patient's immunity which has been produced as a result of previous disease.

Temperatures as high as 107° F. (41.6° C.) are tolerated very well in most instances and 6 hours of heat at 107° F. seems to be sufficient. Of course, there are many drawbacks to this method of treatment. In the first place, it is an ordeal, is expensive, necessitates loss of time, and advertises the patient's disability.

The *danger* of the treatment cannot be overemphasized because there is a distinct one and deaths have been reported in the course of the treatment; however, there is no question about its value in the proper hands and with the patient properly hospitalized.

Perhaps one of the saddest pictures presented to the clinician is that of *gonorrheal vaginitis* in young children. These cases have been extremely virulent; they have been the bane of chil-

dren's hospital wards, and the treatment has been most unsatisfactory. A rather unusual observation and one that has been verified on many occasions is the apparent disappearance of the disease at or near the age of puberty. However, this apparent automatic cure should not be waited for in the treatment of the disease. Due to the extreme contagiousness of this disease, these children should be very carefully isolated in all institutions to prevent the rapid spread of the contagion. The nurses who care for these children should also be isolated and prevented from caring for other children in the institution. A very definite problem is presented in the prevention of this disease where there are other female children in the home and where the patient is cared for at home.

The treatment heretofore has been usually local and reasonably painful. **Suppositories of silver nitrate, mercurochrome** and other **urinary anti-septics**, together with **warm vaginal douches of boric acid and permanganate solutions** have been the routine.

R. M. Lewis and E. L. Adler (J. A. M. A. 106:2054 (June 13) 1936) in 1933 described the administration of **estrogenic substance** as a practical method of treating this disease in children. Eight cases treated at that time and in this manner, with marked success, were reported. The fact was established that sufficient estrogenic substance given to girls would bring about a temporary maturation of the undeveloped vaginal mucosa. Since the publication of this article, several observers have used this form of treatment with varying results, many of which have been almost brilliant. Of course, it must be remembered that in this infection the cervix rarely, if ever, becomes involved. If *endocervical infection* is found in the unusual case, it must be **cauterized**.

In the work done by the authors, the criterion for a diagnosis of *gonorrheal vaginitis* has been the finding in the vaginal smear of Gram-negative diplococci morphologically resembling gonococci. In treating these cases, **estrogenic substance in ethylene glycol** given hypodermically was very effective in large doses—2400 units daily. Any dosage under this has not proved very efficacious. The use of vaginal suppositories of 1000 estrogenic international units is a very effective treatment. If the patient is going to improve, the improvement is noted in 14 to 18 days, the estrogenic substance changing the vaginal secretion from alkaline to acid. This is easily determined and if the secretion does not become acid, the dosage is inadequate. No ill-effects are encountered and the treatment is safe and harmless.

**HYDROCELE.**—G. H. Ewell, C. R. Marquardt and J. C. Sargent (Urol. and Cutan. Rev. 40:386 (June) 1936) have been treating hydroceles by the **injection method**. They have injected 64 hydroceles in 58 patients with excellent results, with epididymo-orchitis as a complication in 5 cases. The *technic* of the injection is:

The scrotum is washed with soap and water, the area painted with **tincture of iodine** and the point of puncture infiltrated with **procaine hydrochloride**. An 18- to 20-gauge needle is introduced by tunnelling under the skin. This is done to prevent leakage of the quinine solution. The needle is introduced well into the sac as when it is emptied the point of the needle is apt to pull out of the sac. At the present time the writers are working on the development of a trocar together with the use of a two-way stopcock which makes aspiration and emptying of the hydrocele sac relatively easy even through such a small gauge needle. The fluid is thoroughly aspirated and the scrotal contents palpated for evidence of tumor or tuberculosis. The fluid is examined microscopically for pus or blood. The initial dose usually has been 2 c.c. ( $\frac{1}{2}$  dram) of **quinine**

**hydrochloride** and **urethane**. Fluid usually accumulates after the first injection. The treatment is then repeated in one week, at which time the amount of quinine solution is increased to 3 or 4 c.c. ( $\frac{3}{4}$  to 1 dram), depending upon the size of the hydrocele. If, following the second injection, the fluid reaccumulates and is not spontaneously reabsorbed within 3 weeks, the treatment is repeated. Should the fluid again accumulate, 3 weeks' time is allowed to elapse, when the treatment is repeated. In many cases, one injection usually suffices. However, 2, 3, or 4 injections may be necessary. The reaspirated fluid in most cases is hazy and contains fibrin. At the end of a week, if the testicle is moved in the scrotum, there is a crepitant feeling not unlike the friction rub in pleurisy. Should epididymo-orchitis occur, as it did in 5 cases observed, the time interval between injections is lengthened to allow the inflammatory process to subside. A subsequent injection in one case caused no recurrence of the epididymo-orchitis.

**KIDNEY. — CALCULI.**—During the last year much work has been done on the cause of renal calculus by many investigators. The relation of the parathyroid gland to urinary lithiasis is emphasized by J. D. Barney and E. R. Mintz (Brit. J. Urol. 8:36 (Mar.) 1936). They believe that from 4 to 5 per cent. of all cases of urinary stone are caused by hyperparathyroidism. The important diagnostic point is the determination of blood calcium and phosphorus. Serum calcium above 11 mg. per 100 c.c. and serum phosphorus below 3.5 mg. per 100 c.c. should arouse suspicion of a parathyroid tumor. It must be remembered that in treating stone in the kidney due to hyperparathyroid tumor, the disease is a generalized metabolic disturbance. In their experiences it is much better to **remove the parathyroid tumor first and the stone later**. Of course, this procedure may have to be reversed if one or both kidneys are badly damaged or blocked by stone.

In the *prevention of the recurrence* of renal calculi, C. C. Higgins (Surg.

Gynec. and Obst. 63:23 (July) 1936) feels that a high vitamin A alkaline or acid ash diet should be prescribed following operation, the constituents of which depend upon the hydrogen-ion concentration of the urine and the chemical constituents.

**RENAL INFECTIONS.** — Coccal infections of the kidney, particularly those that involve the renal cortex, are totally different from those presented by bacillary infections. Almost always the urine is macroscopically clear, although microscopic examination may reveal some erythrocytes, a few pus cells, and some cocci. Many of these coccal infections start primarily in the skin and the *Staphylococcus aureus*, which is usually the causative factor, is carried *via* the blood stream to the cortex of the kidney, where either a cortical abscess or a carbuncle develops, depending entirely on the size of the vessel or vessels blocked by the embolus or emboli. Depending, of course, upon the virulence of the organism and the relative resistance of the patient, the disease may be fulminating or peracute, acute or subacute, and, occasionally, chronic. E. Beer (J. Urol. 35:491 (May) 1936) reviews a series of 104 cases. Many of these cases are particularly helpful in explaining the relation between cortical abscess and perinephritic abscess, while others are very instructive in connection with diagnosis and treatment.

Beer says that there are many helpful aids in arriving at this *diagnosis*. Many cases have had cutaneous infections which occurred weeks or months before the present illness. Fever, leukocytosis and clear urine are valuable diagnostic aids. Jarring over the lumbar region may produce pain. Enlargement of the kidney is unusual. X-ray examination may reveal obliteration of the edge of the psoas muscle on the affected side and

a curvature of the spinal column in the opposite direction. Ureteral catheterization will demonstrate that the kidney is not obstructed. This is important, as renal obstruction may cause curvature of the spinal column and obliteration of the shadow of the psoas muscle. The pyelogram, more frequently than is generally supposed, will reveal a deformity of the renal calyces, with or without changes in the contour of the renal pelvis.

As far as *treatment* is concerned if the diagnosis is made early, **incision** and **drainage**, and **decapsulation *in situ*** usually suffice to cure the condition. In view of the fact that in occasional cases there are multiple cortical abscesses, it is selfevident that a complete decapsulation is advisable.

The same observer, E. Beer (J. A. M. A. 106:1063 (Mar. 28) 1936), also states that the characteristic symptoms of this disease are a rise in temperature with or without chill, with pain in one or both lumbar regions. On physical examination the kidney usually cannot be felt, and if palpable, strange to say, it may be movable. There is regularly a definite jar or punch tenderness over the involved kidney. If the elevation of temperature continues, there is a progressive, often impressive, loss of weight and a progressive anemia. The patient becomes pasty-looking and suggests sepsis. Leukocytosis is almost always present while the patient has fever. In addition, the functional tests of the kidney and the blood examination for retention products are liable to be negative. In practically all these cases at their inception, it is essential to rule out an acute, infected, completely obstructed hydronephrosis.

Many of these cases extend to the perirenal tissues and perinephritic abscess is not an uncommon occurrence. J. Duff (Urol. and Cutan. Rev. 40:86



(Feb.) 1936) emphasizes that there is no formula for diagnosing a *perinephritic abscess*. The history of a recent infectious disease, furunculosis, or other infected focus anywhere in the body, combined with the proper evaluation of the symptoms, which are pain and tenderness, in the costovertebral angle, spasm of the lumbar muscles, elevation of temperature, rapid pulse, gastrointestinal distress, prostration and a high leukocytosis should cause suspicion of a perinephritic abscess. Urological examination is usually negative as in the cortical renal infections. The *treatment* is surgical with prompt **incision and drainage**.

It has been necessary to change completely opinions concerning the *ability of the kidney*, even though badly diseased, to sufficiently *rehabilitate itself* under proper therapy and treatment so that it may carry on its life-saving function. Many a kidney whose ureter has been completely blocked off for varying periods of time will, upon relief of the obstruction, virtually return to its normal functioning capacity. Many a kidney found to be completely useless by all of the renal tests which have been devised has, months later, following correct therapy, been returned to normal function. L. Raff (*Ibid.* 40:727 (Oct.) 1936) calls this cessation of renal function and later return to normal as "hibernation." A case is cited in which complete obstruction by an impacted stone in the ureter occurred. There was no excretion or function of the kidney over a considerable length of time, and upon removal of the obstruction there was gradual return to normal kidney function.

In the *differential diagnosis of renal colic*, allergic reactions as a cause of some of these must be considered. Many cases of renalgia may be directly traced to the sensitivity of the urinary tract

to certain drugs, foods, or other substances. H. A. Levin (*Ibid.* 40:617 (Sept.) 1936) cites such a case where the patient was hypersensitive to citrous fruits, with hematuria at one time and renal colic due to ureterospasm at another. The hematuria is attributed to a purpuric eruption in the genitourinary tract. It may be brought out in a careful history, where, after complete urological survey a diagnosis cannot be made, that the individual may be allergic to certain things. If so, treatment attempting to remove the patient from the influence of various substances to which he may be sensitive should be tried before further attack is made upon the urinary tract. Certainly, it is true that the muscles of the pelvis and the ureter can be allergically thrown into spasm. The author has two patients who always develop renal colic, one following the ingestion of Frankfurters and mustard, the other following intercourse of a prolonged nature. The latter patient also suffers from asthma. Ureterospasm could be demonstrated by cystoscopy in both cases. The differential diagnosis always requires cystoscopic and x-ray examination, and where no etiological factor can be found for the symptom, a careful history may reveal that an allergic reaction is the cause of some forms of hematuria and some forms of colic of sufficient intensity to stimulate calculous disease.

**NEPHROSIS.**—The classification of diseases of the kidney has been a rather difficult problem mainly because the clinical classifications could not be made to balance with the pathological findings. As a result of this, many classifications of renal disease have been attempted. Perhaps the one most universally used is that of Volhard and Fahr. E. Hess (*South. Med. and Surg.* 98:29 (Jan.) 1936) offers a new classification which makes it possible to place together any

clinical and pathological entity. As the definition of the word nephrosis means any disease condition of the kidney, it should not be used as a term to designate the degenerative lesions of the kidney, but should be used as a main heading to designate any pathological condition. For this reason, the following classification has been devised which covers and adds to and, the writer believes, simplifies that of Volhard and Fahr.

Volhard and Fahr's classification is incorporated into the one which is offered and in which any clinical or pathological renal entity can find a logical position regardless of the mixed pathology. Immediately the dominant clinical entity will be qualified. The main heading of nephrosis is submitted as proper because this term means "any diseased condition of the kidney" and under this general classification come the principal subdivisions: (1) Nephrostasis, (2) nephrotoxicoses, (3) nephrophlegmasias, (4) nephrectasias, (5) nephroscleroses, (6) nephro-anomalies, and (7) nephro-neoplasias.

1. Nephrostasis:
  - (a) Orthostatic albuminuria.
  - (b) Congestive albuminuria.
2. Nephrotoxicoses:
  - (a) Acute—
    - (1) Toxic.
    - (2) Lytic.
  - (b) Chronic.
  - (c) Terminal. Contracted kidneys without increase in blood-pressure or with increase in blood urea and creatinin.
3. Nephrophlegmasias:
  - (a) Diffuse glomerulonephritis (increased blood-pressure and bilateral).
    - (1) Acute (with or without edema).
    - (2) Chronic (with or without edema and without renal insufficiency).
    - (3) Terminal (with or without edema, but with renal insufficiency. A degeneration of the epithelial cells).
  - (b) Focal nephritis (without increased blood pressure. May or may not be bilateral):

- (1) Glomerulonephritis:
  - (a) Acute.
  - (b) Chronic.
- (2) Interstitial nephritis (septic).
- (3) Embolic nephritis (focal).
- (c) Pyelonephritis:
  - (1) Acute (bilateral or unilateral, with or without stasis or obstruction).
  - (2) Chronic (unilateral or bilateral, with or without stasis due to obstruction).
  - (3) Terminal (unilateral or bilateral, with or without stasis due to obstruction).
4. Nephrectasias:
  - (a) Congenital or acquired:
    - (1) Hydroectasias (bilateral or unilateral).
      - (a) Acute—always obstructive.
      - (b) Chronic—always obstructive.
      - (c) Terminal—always obstructive.
    - (2) Pyoectasias (bilateral or unilateral):
      - (a) Acute—always obstructive.
      - (b) Chronic—always obstructive.
      - (c) Terminal—always obstructive.
5. Nephroscleroses:
  - (a) Benign hypertension (sclerosis of renal vessels and sympatheticotonia).
  - (b) Malignant hypertension (sclerosis plus nephritis, cardio-vascular-renal disease).
6. Nephro-anomalies:
  - (a) Aplasia (unilateral or bilateral).
  - (b) Hypoplasia (unilateral or bilateral).
  - (c) Fetal-lobulated (unilateral or bilateral).
  - (d) Double kidneys (unilateral or bilateral).
  - (e) Horseshoe kidneys.
  - (f) Cystic kidneys (unilateral or bilateral):
    - (1) Multilocular.
    - (2) Unilocular.
7. Nephro-neoplasias.

It is to be noted that since the advent of insulin, patients with diabetes no longer die from starvation or coma, but from vascular sclerosis and usually with cardiac or renal failure. Even in these cases the differential diagnosis can and possibly should always be made by a competent urologist.

In conclusion, there is no renal condition that cannot benefit diagnostically, prognostically and therapeutically by a complete urological survey by a competent urologist.

**RENAL TUBERCULOSIS.—Diagnosis.**—It is very important to recognize that tuberculosis of the kidney is rather a common condition *in children*. It occurs in infants, children, and adolescents rather frequently and many cases of adult renal tuberculosis have either had silent tuberculous lesions in childhood or active childhood renal tuberculosis which may or may not have escaped the attention of the attending physician. C. P. Mathé (Surg. Gynec. and Obst. 63:283 (Sept.) 1936) discusses this subject in detail, reporting many personal cases. He emphasizes the importance of suspecting renal tuberculosis in all children suffering from chronic cystitis, persistent pyuria and relapsing pyelitis. In children presenting persistent cloudy, opalescent, acid urine, which, when subjected to examination, does not reveal the organisms usually encountered in pyelonephritis and cystitis, the tubercle bacillus should always be suspected. Progressive cystitis sets in, accompanied by frequency, urgency, ardor, persistent or recurrent hematuria, and nocturnal incontinence. Dull pain in the lumbar region and renal colic due to stricture or the lodging of caseous thrombi in the ureter may occur. The kidney may become enlarged and tumefaction can be palpated in the upper abdomen. In addition, there are other general symptoms of tuberculosis, such as anorexia, fever, loss of weight, diminution in strength and vigor, and night sweats. The diagnosis in the majority of cases has been made after nephrectomy for a supposedly pyonephrotic kidney.

It is important to make a complete urological survey in infants and chil-

dren presenting pyuria which persists longer than 4 weeks despite intensive therapy consisting of alkalization and acidification of the urine and the internal administration of urinary antiseptics. With the modern cystoscope, children as young as 4 months can easily be cystoscoped. Bugbee has performed successful cystoscopy and ureteral catheterization in a girl aged 15 days, and a boy, aged 3 months. Pyelography will demonstrate the extent of renal damage. In some of these patients, of course, the diagnosis is very difficult, but if complete urological examination is made on every patient with the foregoing symptoms, there is no question that a proper diagnosis in given cases can be made.

**Treatment.**—The treatment of *unilateral tuberculosis* in infants and children is the same as for adults, namely: early **nephrectomy**. The treatment of *bilateral renal tuberculosis* is, of course, often limited to general **hygienic dietary measures** and probably is better carried out in a sanatorium than in a general hospital or in the home. Occasionally, clinical quiescence and auto-nephrectomy may occur in the unilateral type of the disease.

**PROSTATE.—HYPERTROPHY.**—**Treatment.**—Ever since elderly men have been disturbed by hypertrophy of the prostate, experimental work has been carried on in an endeavor to find ways and means of relieving bladder neck obstruction due to this peculiar entity. Various and sundry operations have been devised and have met with more or less success in mechanically relieving these patients.

Many years ago, the late J. William White, Professor of Surgery at the University of Pennsylvania, discovered that certain types of prostatic obstruction were relieved in men who, for some reason or other, were obliged to subject

themselves to castration, and he advocated and believed that there was something in the testicular secretions which stimulated prostatic growth. He advocated castration for the hypertrophied prostate for a number of years, only to find that in the vast majority of cases this treatment proved to be unsuccessful. That he was a very close observer as well as a brilliant surgeon, is borne out by some of the more modern research activities along the lines of hormonal stimulation and its influence on hypertrophy of the prostate.

W. E. Lower (Cleveland Clin. Quart. 3:11 (Jan.) 1936) in 1928 began to experimentally attempt a logical explanation for the etiology of hypertrophy of the prostate. He made a preliminary report in Atlantic City in 1935 and presented the results of treatment in 40 cases of benign prostatic hypertrophy. Since that time 36 additional cases have been added. He frankly states that no suitable method of assay has yet been developed. It is impossible, therefore, to determine what chemical fraction of the glands contains the hormone "inhibin," and equally as difficult to know whether or not all the preparations were of the same standard strength. His treatment consisted in giving the patients the equivalent of 60 Gm. (2 ounces) of **fresh beef testicular substance** daily after desiccating *in vacuo* at 60° C. The substance was administered by mouth. He feels that the treatment is applicable in those prostatic hypertrophies of moderate consistency as determined by rectal palpation. Some of his patients had complete retention of urine and others did not. Some improvement of the symptomatology should be expected at the end of 2 weeks. The maximum improvement is 6 weeks. It is interesting to observe the reports.

The average age of the patients was 67.0 years, the youngest in the group

| Type                             | Improved and Free From Symptoms | Unimproved | Total |
|----------------------------------|---------------------------------|------------|-------|
| Simple bilateral hypertrophy.... | 14                              | 10         | 24    |
| Trilobar hypertrophy.....        | 17                              | 9          | 26    |
| Middle lobe hypertrophy.....     | 4                               | 4          | 8     |
| Not specified....                | 13                              | 5          | 18    |

was 54 and the oldest 77 years of age. The longest duration of symptoms in the improved cases was 2.01 years and in the unimproved cases 5.1 years.

Concerning the **hormonal treatment** of prostatic hypertrophy, D. van Capellen (Brit. J. Urol. 8:45 (Mar.) 1936) writes that he can report on 50 cases treated by an oil solution of **hombreol**, intramuscularly. In 50 per cent. of the cases he believes that his patients are sufficiently improved that he can speak of complete recovery, while in the other 50 per cent. there was only a slight improvement or complete absence of therapeutic effect. He insists that the correct dose must be found by experiment and that it is absolutely free of danger. These patients treated by **hombreol** and who are improved clinically, do not show any diminution, however, in the size of the gland.

There is no doubt that in certain types of congestive prostatic hypertrophy, the treatment may benefit a few patients. However, more work must be done to verify the findings already discovered and it appears, from a careful study of the effects of glandular therapy thus administered, that it will be a long time before the obstructive prostatic patient can be treated by hormonal substances rather than operation.

**CARCINOMA.—Treatment.—** Since about 25 per cent. of all hyper-

trophies of the prostate in elderly men are complicated by malignancy or are frankly malignant, the question of diagnosis and treatment is one of grave importance.

Young has strongly urged radical **perineal prostatectomy**. Other operators use permanent **suprapubic cystostomy** and others treat the patient with **radium** and **transurethral resection**, while Charles H. Mayo has made the statement that whatever is done for carcinoma of the prostate, it probably will be wrong. Emphasizing the various methods of diagnosis and treatment, H. G. Bugbee (Pennsylvania M. J. 39:665 (June) 1936) writes that every case warrants a most careful study entered into without bias and without a preconceived plan of action before analyzing the individual facts. If possible cures are estimated from a 3- or 5-year basis, in selected cases, *i. e.*, those in which the carcinoma has not invaded the tissues beyond the reach of radical excision, operation, resection, or radiation, or a combination of these methods may give a fair percentage of success over such a period of time.

The urologist should have an open mind regarding the possible benefits to be derived from each method of treatment and in the light of broadening experience select without prejudice the procedure which gives promise of the best chances of relief to the individual, remembering that certain operations may readily prove to be mutilations, that by such the growth may become activated and generalized, and that in certain instances no treatment may be the most warranted and humane procedure. Certainly, in **resection** a procedure has been added to the possibilities of the urologist which gives much comfort without extensive surgery. Only time will show how permanent this relief may prove to be.

**TRANSURETHRAL RESECTION OF PROSTATE.**—The literature is again filled this year with discussions of the results following transurethral resection of the prostate, and there is no question in the minds of most men that this method of treatment is the choice in *carcinoma of the prostate*, *sclerosis of the bladder neck*, and small median lobes. Many men prefer complete enucleation by the suprapubic or perineal method in all hypertrophied prostates larger than Grade II. The advantages of resection are thus summed up by W. J. Engel (Cleveland Clin. Quart. 3:101 (Apr.) 1936). The two chief advantages of resection are that there is less risk to the patient and the morbidity is diminished.

1. Less risk to the patient. Only 8 fatalities have occurred in 453 cases, a mortality rate of 1.7 per cent. Four deaths occurred in the group of 391 benign cases, a mortality of 1.5 per cent. and 3 deaths occurred in the group of 62 carcinomas, a mortality of 4.8 per cent. Most of the fatalities were observed in the earlier cases and no deaths have occurred in the last 206 consecutive cases of all types. It must be remembered, too, that the whole group includes many patients who were over 80 years of age and whose general condition would have precluded any other type of surgery. No attempt has been made to select only the good risk patients for this operation.

2. Diminished morbidity. The average hospitalization was 9 days, the shortest 4 days and the longest 44 days. Convalescence is not prolonged and many of the patients have resumed normal activities 2 weeks after operation. This has a decided economic aspect, in that hospital expense is reduced and the patient is able to resume his occupation earlier.

The *preoperative preparation* has been progressively less rigorous during the 5 years. Originally, routine preliminary catheter drainage was used as for prostatectomy, but all too often elevation of temperature was encountered on the second or third day, which is so commonly seen in patients with an inlying catheter. This practice, therefore, was gradually abandoned, except in the badly infected and atonic, chronically over-distended bladders. In many of the more recent cases the preliminary cystoscopic examination has been dispensed with. After general physical examination, the patient with a typical history of urinary obstruction is admitted to the hospital without any preliminary urethral instrumentation. A *blood urea determination* is made and the kidney function is determined by the *urea clearance test*. If these show no striking variation from normal, the patient is sent to the operating room the following day, given a **spinal anesthetic** and all preparations are made to proceed with the operation. The *resectoscope* is introduced, the bladder and bladder neck surveyed with the observation telescope and, if suitable for resection, the operation is proceeded with. If not suitable (a circumstance not yet encountered since managing cases in this manner), the patient has simply been given the advantage of a cystoscopic examination under anesthesia and, at a later time, prostatectomy is carried out. It is actually true that patients handled in this manner have had less reaction than is occasionally seen following cystoscopic examination or even simple urethral catheterization. It is to be understood that this management applies only to the average uncomplicated cases which constitute, however, a considerable proportion of patients seen.

The *technic* of the operation need not be given here, but it should be empha-

sized that it is not an easy operation to perform and, to one who has done both, it is decidedly a more difficult procedure than prostatectomy. The amount of tissue to be removed varies according to the individual case, but, in every instance, sufficient tissue must be removed to create an unobstructed channel from the trigone of the bladder out to the verumontanum. Personal experience has shown that bleeding is not a troublesome problem and in only one instance has it been necessary to open the bladder suprapubically because of bleeding. This occurred 4 years ago, which was quite early in our experience with the method. Great care must be exercised to prevent injury to the external sphincter. Not a single instance of urinary incontinence has been encountered in the entire 453 cases.

*Postoperatively*, these patients have very little discomfort and minimum sedation is required. The catheter is removed routinely on the second day following operation and the patient is then allowed to get out of bed and to have bathroom privileges. The average patient will experience some frequency and bladder irritability for a few days, but ordinarily this subsides quite rapidly. Usually, the patients are dismissed from the hospital 5 to 7 days following the operation.

These factors are also emphasized by G. J. Thompson and H. A. Buchtel (J. Urol. 36:43 (July) 1936), who review a series of 200 consecutive cases in which more than 25 grams of prostatic tissue has been removed transurethraly, while J. W. Davis (Urol. and Cutan. Rev. 40:26 (Jan.) 1936) states: Transurethral prostatic resection has made it possible to give relief to many patients who could not stand an open operation. To others it has made possible a short period of hospitalization, relief from symptoms, and an early

return to work. These are important factors which have made this operation desirable in the majority of cases. Most urologists believe that transurethral resection is among the greatest of the advances made in surgery in the past decade.

**TESTICLE.—TUMORS.**—According to A. E. Cerf and S. A. Goldman (Urol. and Cutan. Rev. 40:507 (July) 1936), malignant tumors of the testicles occur in 0.5 per cent. of all tumors. Their classification is most unsatisfactory and Hinman states that for practical purposes, the homologous carcinoma (seminoma) and the heterologous teratoma are the only testicular tumors of clinical importance. Differentiation from other scrotal tumors is necessary and determined by exclusion. Gumma of the testicle should always be suspected and if antiluetic treatment gives no immediate response, the growth should be exposed and **removed**. Both **radiation and surgery** are often indicated.

F. Gentil (Arch. ital. di chir. 42:501, 1936) states that *seminomas* are the most common tumors of the testicle and have been frequently diagnosed as sarcoma. Seminomas of the ovary are considered very rare. The preoperative diagnosis of seminomas is often made by the great radiosensitivity of these tumors, and, of course, this is an aid in making the diagnosis. Because of the ease with which the tumor cells may be spread by way of the lymphatics, injury of the involved organ must be avoided in the **operative removal** of the tumor and should be followed by **x-ray irradiation** of both the operative area and the lumbo-aortic region, which is the most frequent site of the first metastases.

**URETHRA.—RUPTURE.**—**Treatment.**—With the advent of the

automobile and the many subsequent accidents, fracture of the pelvis and rupture of the urethra have become more and more common. The diagnosis and the treatment, of course, depends upon whether the rupture is anterior or posterior to the triangular ligament. When the urethral floor is so severely traumatized that continuity is destroyed, the proximal vesical portion is retracted and elevated by the pull of the strong fascial attachments of the urogenital diaphragm. This injury must be considered in every case of fractured pelvis and will happen in many cases where there is no fracture of the pelvis but where the traumatism is directed to the perineum. In the mining districts of the country where crushing accidents are of common occurrence, the method of treatment has been to pass a sound into the perineum from the penile urethra and another through a suprapubic wound to the perineum *via* the prostatic urethra. Incision is then made through the perineum and, by using the sounds as guides, a large catheter is drawn out through the anterior urethra and back through the posterior urethra into the bladder. The tip in the bladder is sewn then to a large suprapubic drainage tube. This splints the urethra and permits two-way drainage. Both the perineal wound and the suprapubic one are then drained. The catheter should be left in for a period of approximately 3 weeks.

V. J. O'Connor (Surg. Gynec. and Obst. 63:198 (Aug.) 1936) offers what seems to be a much more advantageous surgical procedure. He does not claim that the method is original. As may be seen from the accompanying schematic drawings, interlocking sounds are passed simultaneously through the posterior urethra and anterior urethra and joined in such a way that the urethrally-introduced member (male sound) may be fitted snugly into the

sound passed through the bladder neck (female sound), thus permitting the former to be guided safely into the bladder. This prevents opening the perineum which, of course, further complicates the injury.

A No. 22 F soft rubber catheter is then stitched securely over the end of the male sound, and the edges of the

When the catheter has been fixed in the urethra in its proper position, the bladder is closed in the usual manner with a small mushroom catheter in the dome of the bladder for immediate drainage. The urethral catheter is closed for a period of 5 to 7 days, suprapubic drainage being allowed during this time. The urethral catheter is then opened,

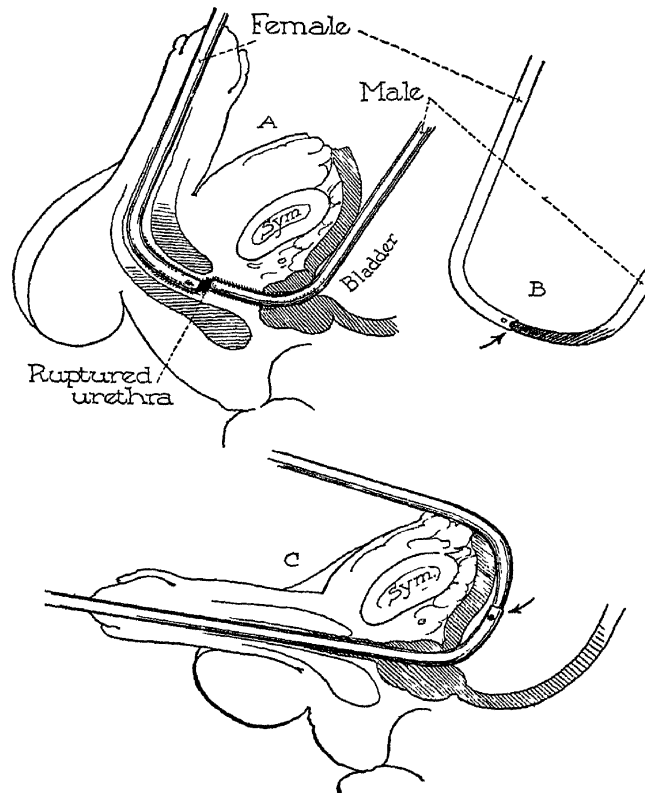


Fig. 1.—A. Illustrates interlocking sounds (designed by G. G. Davis) guided through the urethra and through the vesical orifice until they are properly joined. B. Position before guiding urethral sound into bladder. C. After sound has been guided into bladder. (V. J. O'Connor: Surg. Gynec. and Obst.)

catheter are tied tightly to approximate the taper of the sound closely. This facilitates the ease of drawing the catheter back through the urethra and insures a smooth passage through the friable ruptured portion. This step is an improvement over the method of Davis in which the eyelet portion of the catheter is loosely stitched to the sound, with the possibility that it may pull loose or catch upon the urethral edges during withdrawal.

the bladder is irrigated, and the suprapubic tube is removed. There is rarely any suprapubic leakage of urine after this time, drainage being adequately supplied through the urethral catheter. The latter is removed when the suprapubic wound seems firmly healed, usually on the twelfth to the sixteenth day after operation.

The complete restoration of normal urinary function and the subsequent lack of urethral stricture are the obvious



advantages of this method when the results are compared with those in patients previously operated upon solely through the perineum. These patients require occasional urethral dilatation, to be sure, but they are in no wise the serious potential stricture problems that have been encountered almost invariably after perineal urethrotomy.

**URINARY TRACT INFECTIONS.—Treatment.**—It is a well known fact that renal infections are

hydroxybutyric acid excreted in the urine by this altered dietary intake inhibited the growth of the infecting organism. It had already been recognized that in addition to the change of diet, an increased acidity of the urine was a necessity for successful results. Several authors have reported experiments which showed that bacterial growth in the urinary tract would be inhibited by a concentration in the urine of 0.5 per cent. beta-hydroxybutyric acid and an acidity of the urine of pH 5.2.

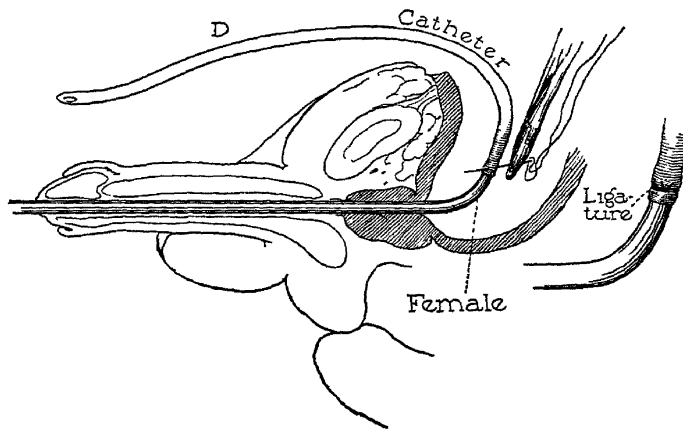


FIG 2.—Method of suturing catheter to "male" sound so that it may be drawn safely through the urethra. (V. J. O'Connor: Surg. Gynec. and Obst.)

among the most common problems encountered by the physician. Many types of organisms attack the renal pelvis and parenchyma. Many of these are secondary to foci of infection at some distant point and it is in these infective cases diagnosed and treated early that many brilliant results are obtained and often surgery is either postponed or prevented. During the past few years a great deal has been written concerning the treatment of renal infections by diets, particularly the **ketogenic diet**. This has been used freely at the various large clinics in the country and A. L. Clark (J. A. M. A. 107:1280 (Oct. 17) 1936) discusses the treatment by the ketogenic diet very thoroughly. Fuller, of London, was the first to discover that beta-

The author gives definite specific information in 3 dietary group plans with the following general instructions:

1. Satisfactory results cannot be obtained unless this diet is followed absolutely as outlined.
2. All food must be measured carefully and accurately. A standard measuring cup, teaspoon and tablespoon must be used.
3. No food or beverage other than that listed is to be taken.
4. Eat no sugars or sweets of any kind. Saccharin, a substitute for sugar, may be used.
5. Coffee, tea and seasonings may be used as desired.
6. Bran wafers must have no food value and may be used as desired.
7. Do not chew gum or tobacco. Smoking is permitted.
8. Water should be taken only in moderate amounts.

9. No cathartics are to be used other than liquid petrolatum or bitter cascara. Magnesia magma or other sweet cathartics will cause failures.

10. Take no medicine unless prescribed by the physician.

11. If you become nauseated while on the diet, omit a meal or two, take a half glass of tomato juice, half an orange or a glass of sour lemonade.

#### MENU PLAN

Include the following foods daily, and in the exact amounts specified:

Eggs—2.

Bacon—4 strips 6 inches long.

Vegetables— $1\frac{1}{2}$  cups.

Whipping cream (extra heavy)— $1\frac{1}{4}$  cups.

Butter or oil mayonnaise—5 tablespoons.

Meat— $2\frac{1}{2}$  ounces, or  $3 \times 4 \times \frac{1}{4}$  inches thick.

Menus 1, 2, 3 and 4 suggest possible combinations. Many interesting menus may be planned, however, when different vegetables are used and eggs and cream are prepared in various dishes.

Nesbit suggested applying the acidosis and ketosis produced by a **starvation diet** to the treatment of infection of the urinary tract. As a result of the observations of many authorities, it has been definitely proven that this type of therapy is extremely valuable in uncomplicated bacillary infections of the urinary tract. **Mandelic acid** in several forms has proven to be an effective urinary antiseptic and should be tried before the ketogenic diet, as it is virtually impossible to treat ambulatory patients effectively by the diet. While, for the most part, the acidification of the urine is specific for bacillary infections, in children it has been used satisfactorily in both bacillary and coccic types of infection. To treat an adult patient from 8 to 10 days requires approximately 100 Gm. ( $3\frac{1}{3}$  ounces) of mandelic acid.

# GYNECOLOGY AND OBSTETRICS

By P. BROOKE BLAND, M.D., and ARTHUR FIRST, M.D.

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## GYNECOLOGY

### BLADDER.—MANDELIC ACID AS A URINARY ANTISEPTIC.—

G. Carroll, B. Lewis and L. Kappel (J. A. M. A. 107:1796 (Nov. 28) 1936) report their clinical experience with 50 cases of *pyuria* treated by mandelic acid. The results obtained indicate that there is a definite value in the drug, superior to all other forms of medication in urinary infections. In a surprisingly large number of cases in which a highly acid urine was obtained, the results were most gratifying.

Apparently the drug is most effective against the colon bacillus and less effective against the staphylococcus, *Bacillus proteus* and *Bacillus pyocyaneus*. Recurrence of pus and bacteria, after discontinuance of the medicine, occurred in some instances but yielded promptly when again administered. Those negative to culture are more likely to remain so than those negative only to pus. In no instance was any toxic effect or impairment of function noted during the use of the drug.

The treatment has been conducted in the following way: The urine was examined microscopically to determine the amount of pus and the morphologic appearance of the infecting organism. Cultures of urine aseptically collected by catheterization were made prior to and following treatment: The acidity of the urine was determined by nitrazine paper (Squibb) and nitrazine colorimeter charts, which offer a very simple and

clinically satisfactory method. The patient was immediately placed on an acid-ash diet and given 2 ammonium chloride tablets, 0.5 Gm. ( $7\frac{1}{2}$  grains), 4 times daily. The acidity of the urine was tested daily and when a *pH* of 5.5 or better was attained, which usually occurred in 24 hours, mandelic acid was prescribed in the following formula: mandelic acid 48 Gm. ( $1\frac{3}{5}$  ounces; sodium bicarbonate 25.6 Gm. ( $6\frac{2}{5}$  drams); distilled water 480 c.c. (16 ounces). A flavoring syrup to satisfy personal preference was added. In some cases nausea, diarrhea or dysuria occurred. This they considered to be due to the ammonium chloride rather than to the mandelic acid, since in changing to sodium biphosphate the mandelic acid could be continued. Wherever an alkaline condition persisted, a careful recheck of the food taken often disclosed the inclusion of orange or lemon juice, spinach, beans, molasses or olives in the diet. When these were removed and the acidifying agent increased, the proper *pH* was established. The medication was continued in most cases for a week following the finding of a negative urine. If a recurrence developed, the régime was repeated.

Rosenheim states that he has been using the ammonium mandelate recently, which makes the urine acid without the necessity of using ammonium chloride. However, sodium mandelate and ammonium mandelate are quite

hydroscopic and decompose. This is particularly true of ammonium mandelate. The mandelic acid is quite stable and the most convenient form for the druggist.

According to the authors the results obtained in some cases of chronic pyuria have been remarkable. Cloudy urine that has resisted all form of medication has become crystal clear in 4 or 5 days.

The authors treated 37 cases of *Bacillus coli* infection, embracing acute and chronic pyelitis, pyelonephritis, vesical diverticula, nephroptosis, renal calculus, prostatic hypertrophy with retention and cystitis. All these became microscopically clear under the treatment. Seven yielded positive cultures.

The average number of days of treatment required to produce negative urines was 7.1. The 7 cases of coccid infections, although improved, were not made sterile. This group is too small to conclude definitely that this organism is altogether resistant, especially when they are reported as being affected *in vitro*.

Of the 6 cases of *Bacillus proteus* infection, only 1 was made sterile. The proteus organism, they find, is most resistant in the urinary tract. Eighty-one per cent. of all colon infections treated resulted in sterile cultures. Practically all cases improved symptomatically and the urines became less cloudy. The authors conclude from this survey that a urinary infection of a colon bacillus type, in which a pH of 5.5 is obtained, may be expected to clear up with the administration of mandelic acid within 4 to 12 days.

The authors emphasize that all these patients were subjected to careful urologic study and the original causative factor in producing the pyuria was recognized and treated in the realization that the pyuria was only one manifestation of the trouble.

**CLITORIS. — CANCER.** — After reporting a case of carcinoma of the clitoris, E. Hausen (Arch. Franco-belges de chir. 35:37 (Jan.) 1936) discusses at length the incidence, etiology, symptomatology, evolution, prognosis, and treatment of the condition. He emphasizes especially the importance of secondary involvement by metastases to the lymphatics. His operative treatment is based upon eradication of the lymph nodes.

Primary cancer of the clitoris constitutes about 4 per cent. of vulvar carcinomas. It is the most malignant form of vulvar malignancy because of the rich blood and lymph supply which favors the dissemination of metastases to the inguinal and pelvic nodes.

The presence of metastases in the lymph nodes has no relationship to the age of the cancer nor to the extent of the involvement. Invasion may occur late or early. Clinical determination of the presence or absence of lymph-node involvement is difficult if not impossible. Histological examination alone will decide this question.

For these reasons, carcinoma of the clitoris, like breast cancer, requires early **radical operation with methodical and complete removal of the lymphatics.** The operation includes two steps: (1) removal of the lymph nodes, and (2) removal of the tumor. Both procedures are preferably carried out at one time if the condition and age of the patient will permit. The author begins his operation by removing the superficial and deep inguinal and the external iliac lymph nodes. If the femoral vein is invaded or if the neoplasm cannot be dissected away from it, the vein is sacrificed. Hausen does not fear gangrene of the leg, as the femoral vein has abundant anastomoses. Severing the femoral vein provides better access to, and facilitates removal of, the retro-

crural nodes. The glands, fat, and neoplasm are removed in a single block.

If circumstances permit, the excision is followed by **postoperative irradiation**, as this considerably increases the incidence of permanent cure.

# **DYSMENORRHEA. — Etiology.**

—S. L. Israel (J. A. M. A. 106:1698 (May 16) 1936) discusses the various theories concerning the etiology of *primary dysmenorrhea*.

The so-called constitutional inferior or the hypersensitive type (Libman) has a definitely increased pain reaction which may color the symptomatology and alter its clinical evaluation.

A neurogenic basis for primary dysmenorrhea has been advanced by some who ascribe the etiology to an abnormal reactivity of the cervical nerves. That nerve irritability or vagotonic spasm of the circular musculature of the isthmus may be a factor is favored by reports of relief through the use premenstrually of antispasmodics, such as atropine, benzyl benzoate and calcium. A successful form of neurosurgical therapy, *i. e.*, resection of the superior hypogastric plexus (presacral nerve), has been evolved. That a full measure of relief follows such nerve resection is not surprising, since the pain-bearing fibers are severed. However, it is a relatively heroic procedure and should be reserved as a last resort in the treatment of primary dysmenorrhea. Others liken the disease to herpes zoster, regarding the ganglions of Frankenhauser as the primary seat of disease and the pain as an expression of secondary neuralgia. In his study of the plexus of Frankenhauser following castration, Kennedy noted degeneration of the ganglion cells characterized by a decrease in the amount of Nissl substance and a diminished number of pheochrome cells. By the administration of estro-

genic principle to castrated animals, Kennedy was able to reserve these changes, the ganglion cells becoming normal.

Because dysmenorrheic patients usually, if not invariably, present other evidences of marked instability of the autonomic nervous system, such as visceroptosis, gastrointestinal spasticity, and irritability of the bladder, primary dysmenorrhea must be viewed as being a local manifestation of a constitutional disease.

The oldest explanation of the origin of primary dysmenorrhea is the one ascribing the pain to mechanical obstruction of the cervical canal. However, it became apparent that not all patients with primary dysmenorrhea present anatomic obstructions and that many patients with acutely anteфлекed uteri are entirely free from menstrual pain.

In view of the newer knowledge of cervical function and the trophic purposes of the cervical nerves, the relief of primary dysmenorrhea following cervical dilatation may be credited to a stimulative effect on the ovaries. Such a result would be analogous to the ovarian reaction produced by mechanical or electrical stimulation of the cervix in experimental animals (pseudo-pregnancy).

Novak and Reynolds attribute primary dysmenorrhea to a premenstrual imbalance of the two ovarian hormones controlling uterine contractions, either an excess of estrogenic substance or a deficiency of the corpus luteum principle. Under such an abnormal endocrine influence, the endometriums of dysmenorrheic women should invariably show a deficiency or a total absence of the secretory phase. That this is usually not the case is shown by a study of the premenstrual endometriums in 20 women with primary dysmenorrhea, 14 of whom

showed normal secretory endometriums (progestin phase).

**Treatment.**—According to Israel (*Ibid.*), the use of **corpus luteum substance** in the treatment of primary dysmenorrhea was first recommended by Novak and Reynolds on the strength of their theory.

Two forms of endocrine therapy have been proposed for primary dysmenorrhea, *i. e.*, **estrogenic substance** and (in the absence of progestin commercially) **urinary gonadotropic substance**. As shown in the present study of 39 patients by the author, both forms of organotherapy are disappointing.

**Urinary gonadotropic substance (antuitrin-S)** administered to 10 patients cured 1 and temporarily relieved 3 of dysmenorrhea.

**Estrogenic principle**, given orally in small doses (**emmenin liquid** or **progynon tablets**) to 16 patients, cured 1 and afforded temporary relief to 3 of the patients.

Estrogenic substance, given hypodermically in large doses (**progynon-B**) to 13 patients, produced no permanent results. Ten patients were temporarily relieved and 3 were totally unaffected by the therapy.

According to A. Altschul (*Ibid.* 106: 1380 (Apr. 18) 1936), **insulin**, if properly used, is entirely safe. It is too early to say definitely whether it is capable of altering the patient's condition so that after its use for some time there will be permanent absence of pain. The reports of its success in this group of cases are gratifying.

In the group of cases here reported, most of the patients were underweight and had a lowered basal metabolic rate. None of them showed stigmas of hysteria or psychoneurosis, or evidence of other endocrinopathies. The blood sugar levels, when taken, were within normal limits. No severe insulin shock was en-

countered. With the exception of case 5, there was no pathologic condition of the pelvis noted, and even in this case, with extensive intraabdominal adhesions and previous salpingoovarian disorder, there was entire absence of menstrual pain during the time of insulin administration.

In 10 of the 12 cases reported, definite relief was obtained with insulin, either premenstrual 5 to 7 days—10 units once or twice a day; or during the pain, 10 units with relief in 20 to 45 minutes. Patient 4 expressed her preference for the premenstrual method of administration, because it removed the anticipation of a painful period. On account of her menstrual irregularity and the pressure of institutional work, she omitted the daily administration before her last period (December, 1935) but gave herself 10 units with the onset of pain. She was completely relieved in 20 minutes.

M. K. Tedstrom and L. E. Wilson (California and West. Med. 44:375 (May) 1936) find a relationship between menstrual hypoglycemia and functional dysmenorrhea. They tabulate the results of their blood sugar studies during menstruation and the results of **extra carbohydrate feeding** in 38 cases. In every case in which the fasting blood sugar was low, *i. e.*, below 80 mg. per 100 c.c., the individual had either menstrual pains of varying severity or complained of marked nervousness, irritability, weakness, extreme hunger or excessive desire for sweets 2 or 3 days preceding menstruation. The treatment of the patients with functional dysmenorrhea associated with a low fasting blood sugar or a low sugar curve during menstruation consisted of extra carbohydrate feedings beginning about 3 days before the onset of the menses and continuing through the first 3 days of the period. It was observed

that better results were obtained if the extra feedings were taken at intervals of 2 or 3 hours during the day rather than larger amounts at longer intervals. **Orange juice** was the usual form of carbohydrate taken. **Karo syrup, dextrose** and **cane sugar** worked equally well. These extra carbohydrate feedings have relieved the premenstrual tension and the menstrual pain in about 80 per cent. of the cases in which they have been tried. Eight patients have been given 25 c.c. of a 50 per cent. solution of **dextrose** intravenously, with immediate relief of menstrual pain. If the pain returns, it is usually slight and easily controlled by extra carbohydrate feedings. Since relief of the menstrual discomfort was also obtained by several patients with a normal blood sugar, it seems wise to try this form of therapy in every case of functional dysmenorrhea.

Through **resection of the presacral (hypogastric) nerve** for the relief of dysmenorrhea and pelvic pain, W. T. Black (Ann. Surg. 103:903 (June) 1936) obtained excellent results in the majority of the 27 cases that he cites. There were 9 cases of the essential and 18 of the acquired type of dysmenorrhea. Fifteen patients suffered from bladder disturbances (dysuria was severe in some and milder in character in others). There were definite pathologic changes in 10 cases. In 14, retrodisplacements were corrected and appendectomy and sympathectomy were performed. Three had a diagnostic dilation and curettage and 2 a cauterization of the cervix, besides the sympathectomy. Postoperative catheterization was necessary in 13 cases. Seven patients in this group had postoperative bleeding in 2 or 3 days (without pain in 6, slight in 1). Three had a single nerve, one a double nerve and the remainder a plexiform arrangement. Excellent results were ob-

tained in 21 cases. A marked improvement was obtained in 5 cases. One patient could not be located. Dysmenorrhea was relieved practically 100 per cent.

Bladder symptoms were relieved immediately, but after a few months some complained of a burning on urination. This could be due to a recent gonorrheal infection, although the nerve supply to the urethra must be considered as a possible cause of continued complaint. Constipation was not relieved in a number of instances; however, in some it was corrected. The sympathetic nerve supply is so variable that failure to relieve constipation can be ascribed to this cause in some cases. Metrorrhagia was relieved in 2 cases. **Presacral sympathectomy** in addition to **removing** and **pelvic pathologic changes** in suitable cases of pelvic pain has increased the percentage of cures.

**MENOPAUSE.—Treatment.**—According to S. Teneff (Ginecologia 1:851 (Aug.) 1935), the treatment of ovarian insufficiency by **transfusion** is more rational and physiological than the use of urine or commercial ovarian preparations. Since 1932 the author has treated 12 patients suffering from serious disturbances of the surgical menopause with transfusions of from 200 to 300 c.c. of blood from women during pregnancy, the premenstrual, menstrual, or intermenstrual periods, and from male donors. The patients ranged in age from 28 to 43 years and had been subjected to bilateral oöphorectomy from 6 months to 4 years previously.

The author concludes that the blood of donors during pregnancy and the premenstrual, menstrual, and intermenstrual periods has about the same efficacy, causing disappearance of the symptoms for 2 or 3 months. Its most striking effect is on the vasomotor phenomena. The

blood of male donors attenuates but does not abolish the disturbances. The action of the transfusions is attributed not only to the introduction of large quantities of ovarian hormones, but especially to the hormones of other endocrines which, by their presence and independently of their quantity, correct the disequilibrium due to castration at first temporarily and finally completely. As is demonstrated by the results of the use of male donors, the female sex hormones are not necessary if hormonal activity is reestablished by the other hormones transfused.

In the **radium** treatment of *menopausal hemorrhage* K. J. Anselmino (Zentralbl. f. Gynäk. 60:547 (Mar. 7) 1936) notes that at his clinic the dose has been steadily decreased from as high as 3000 mg. element hours in 1928 to around 1000 mg. element hours in recent years.

He always precedes the radium treatment by a **curettage**. He then introduces 50 mg. of radium element, which is deposited in units of 10 mg. in 5 silver tubes 0.1 mm. in thickness, which in turn are enclosed together in a brass container that has a wall thickness of 1.5 mm. In evaluating the results that were obtained at his clinic, he finds that the cases that have been treated with doses from 800 to 1200 mg. element hours react quite favorably to the treatment, in that there was only 1 failure in 50 cases.

The higher the age of the woman at the time of the treatment, the better the effect of the rays, *i. e.*, smaller doses produce the desired effect. The more moderate doses have the advantage of not causing complications, there are no signs of intoxication, and the symptoms of abolished function are mild, *i. e.*, somewhat like those of the normal menopause. Many women complain of leukorrhea after the radium treatment, but

this disorder usually disappears in several weeks or months. He employs radium as a rule only in women over 42 years of age who have climacteric hemorrhages. In these he usually does not differentiate whether a glandular hyperplasia exists or not. However, in the milder cases he usually limits the treatment at first merely to a curettage. Thus the radium treatment is usually reserved for the more severe cases. For *younger women* he considers surgical intervention in the form of a **supravaginal amputation** or of a **fundus resection** advisable, in that such interventions do not affect the general organism as much as an exclusion of the ovarian function with radium therapy.

#### **MENORRHAGIA. — Treatment.**

—It is pointed out by E. Klasten (Wien. klin. Wchnschr. 48:1509 (Dec. 6) 1935) that a number of investigators have tried **insulin** in the treatment of menstrual disturbances and that he has resorted to its use as a *prophylactic*. He found that this treatment normalized the flow in some cases of profuse menstrual bleedings and particularly in prolonged bleeding. He considers it especially important that the treatment was helpful in cases of polymenorrhea. It proved possible to prolong the interval from 14 to 20, 24, and finally 28 days. The interval was normalized and the period of bleeding was shortened in 12 of 15 patients with *polymenorrhea* and *hypermenorrhea*, but the intensity of the hemorrhage was influenced only in half the number. In 12 cases of juvenile hemorrhagic metropathy the results were likewise favorable, but in preclimacteric hemorrhagic metropathy the effect was not so good, in that only some of the patients responded. The latter were usually women who had undergone surgical treatment for gastrointestinal ulcer or for cholelithiasis. All had lost weight



and this emaciation was accompanied by menstrual disturbances, *i. e.*, these cases were characterized by secondary, insulogenic menstrual anomalies.

Another group of women in whom polymenorrhea and hypermenorrhea were favorably influenced by insulin therapy were those who had a hereditary history of diabetes or later developed diabetes. Women of the preclimacteric period with hemorrhagic metropathy who did not have the aforementioned symptoms (emaciation, metabolic disturbances, cholecystopathy and so on) did not respond so well to insulin treatment.

The insulin *dosage* was adapted to the body weight, the age and the blood sugar value. Generally, the daily dose varied between 15 and 30 units, but in some instances as much as 40 or 50 units was given. The injections were begun 5 days before the expected menstruation and were continued for 4 or 5 days. The author points out that he found insulin effective also in 2 women with emaciation, anorexia and amenorrhea. The mechanism of the insulin action is extremely complicated. He mentions the metabolic component, the regenerative effect, the influence on the sympathetic nervous system, on the process of follicle maturation, and the formation of the corpus luteum. An influence on the anterior lobe of the hypophysis is likewise possible.

**MENSTRUATION.—Effect of Estrogenic Substance.**—The effect of estrogenic substances upon menstruation was investigated by B. Zondek (Wien. klin. Wchnschr. 49:455 (Apr. 10) 1936), who found that the normal menstrual cycle can be inhibited by their administration. To produce this result it is necessary to administer at least 70,000 mouse units, but if 200,000 or 300,000 mouse units is given, the result

is more certain, *i. e.*, at least one-third of the quantity of substance necessary for the proliferation of the uterine mucosa must be administered to produce amenorrhea. The earlier the administration is begun (best immediately after menstruation), the more certain is the action. The duration of the resulting amenorrhea is not in proportion to the dose. The menstruation is retarded by from 6 to 70 days. Estrogenic substance can inhibit or entirely prevent the premenstrual proliferation of the uterine mucosa. If estrogenic substance (at least 200,000 mouse units) is given at the premenstrual phase, the further proliferation of the uterine mucosa is retarded. Estrogenic substance inhibits also the development of the corpus luteum, so that a parenchymatous degeneration and shrinkage may be the result. The gonadotropic hormones of the anterior lobe of the hypophysis are involved in the mechanism of the inhibition (perhaps shift in the proportion of follicle stimulating to luteinizing factor). This is indicated by the increased elimination of the follicle stimulating factor in the amenorrhea produced by the administration of estrogenic substance. The author emphasizes that menstruation is a complex hormone process in which the gonadotropic hormones of the anterior hypophysis as well as the ovarian hormones play a part. He believes that the production of temporary amenorrhea by estrogenic substance is of clinical value.

**Effect of Exercise.**—It has often been claimed that athletic activity is beneficial during the menstrual flow. M. Nizza (Ginecologia 2:153 (Feb.) 1936) reports the results of a study of 50 girls who were actively participating in light athletics, such as jumping, running, basketball, swimming, canoeing, skiing, and tennis.

The girls ranged in age between 17 and 22 years. The youngest was 15 and the oldest 24. The author divides them into two groups on the basis of their training.

In the *first group* there were 30 girls who had been training 4 or 5 hours a week for not more than a year. Among these were 10 girls who abstained from training during the menses. None of the latter experienced disturbances of menstruation. One even stated that athletics relieved the dysmenorrhea and hypermenorrhea of which she had been suffering since puberty. The remaining 20 girls in the first group participated in athletic training also during the menses. Of these, 9 had no complaints, 8 complained of an increased sense of fatigue when training during menstruation, and 3 stated that during the period their vigor was increased. However, one of the latter stated that during menstruation she experienced an increased sense of fatigue the day following training and that she had been repeatedly amenorrheic.

In the *second group* were 20 girls who had been training for from 7 to 10 hours a week over a period of several years. Among them were girls who had participated in various Olympic contests. Training was continued even during the menses. Eleven girls did not notice any disturbances, but 9 stated that they experienced a greater sense of fatigue when training during menstrual periods. Of the latter, 5 complained of pain in the lower quadrants of the abdomen during menstruation, and 2 of menorrhagia, headaches, dizziness, and nausea. Five of the girls in the second group developed various disturbances of menstrual function, such as menorrhagia, early monthly onset, and prolonged flow during their athletic career.

The author concludes that girls indulging in athletic activities during

menstruation are apt to develop disturbances of this function, because the pelvic congestion which occurs at the menstrual periods tends to become aggravated by increased muscular activity. He suggests, therefore, that activity requiring excessive muscular work be completely avoided during menstruation.

#### **INTERMENSTRUAL PAIN.**—

By periodic intermenstrual pain is meant the recurring discomfort which some women feel half-way between their menstrual period. Many women can foretell to the day the onset of the next menses from the date of this periodic intermenstrual pain.

L. R. Wharton and E. Henriksen (J. A. M. A. 107:1425 (Oct. 31) 1936) report 61 cases of periodic intermenstrual pain. Thirty were subjected to laparotomy.

In 9 patients who were operated on while suffering intermenstrual pain there was evidence that ovulation had just occurred ruptured follicles with varying amounts of free blood in the pelvis.

**Removal of one or both ovaries** is the only operation that has uniformly eliminated the recurring pain. This has been the general experience of former observers. **Excision of the acute ruptured follicle or corpus luteum** has in some cases brought relief.

Supravaginal hysterectomy in 2 cases had no effect. In these cases the endometrium was normal.

Curettage, cauterization of the cervix, excision of old Graafian follicle cysts and appendectomy have rarely affected the syndrome.

The pain seems to occur only during ovulation. They have never seen it before the menarche or after the menopause. If the ovaries are inspected during the pain, recent ovulation is found.

The syndrome is not always persistent. In some cases it disappeared as unexpectedly as it came, untreated or after

measures which would ordinarily afford no relief. The authors feel, therefore, that at times painful ovulation may be due to some temporary change, perhaps a mechanical, inflammatory or circulatory disturbance, and that it disappears when this situation is corrected. Thus, occasionally the syndrome has disappeared after the birth of a child, after a curettage, after the insertion of a stem pessary or even after rest in bed.

The authors have found no pathologic basis or explanation of this syndrome; almost invariably the pelvic organs are normal in every particular.

Women who have painful ovulation usually are fertile and bear healthy children. Therefore, the syndrome does not interfere with the production of normal ova. It is an inconvenient syndrome, but interferes with the patient's health only when the pain is severe or accompanied by profuse hemorrhage from the Graafian follicle.

**OVARY.—TUMORS.**—W. Schiller (Arch. f. Gynäk. 160:344 (Dec. 19) 1935) points out that the question as to the manner of the *transformation of the sex characters* under the influence of masculinizing tumors can be answered only on the basis of the observations and opinions regarding the determination of sex. He points out that, whereas for a while it was believed that sex is determined by the hormones, it has been asserted also that the primary fixation of sex takes place on the zygotic, chromosomal basis. Cytologic studies on the sex cells indicated the possibility of a progamous and of a syngamous fixation of sexuality; to be sure, the complete postembryonal development and maturation of the congenitally conditioned sex organs and sex characters is effected by the influence of hormones. The author points out that at present it is generally believed that, although

the hormones exert a protective influence on the sexuality, the primary fixation of the specific sex characters nevertheless is lodged in the chromosomes. However, experiments have revealed that this so-called zygotic determination is by no means entirely fixed and unchangeable.

In giving his attention to the masculinization of women under the influence of some ovarian tumors, the author considers it doubtful that the progamously or syngamously determined chromosomal constitution can be influenced later by internal or external factors. He considers it more likely that the hormones produced by the tumor stimulate and develop latent primordiums. He stresses that a causal connection between tumor and masculinization is definitely proved only if the symptoms of masculinization disappear following the extirpation of the tumor. Considered from this point of view, there are only 3 types of tumors that are connected with masculinization: (1) ovarian tumors the structure of which resembles the male gonad, (2) lutein tumors, and (3) adrenal tumors.

**Types.**—E. Novak and L. A. Gray (Am. J. Obst. and Gynec. 31:213 (Feb.) 1936) note that while precocious puberty may be due to various other endocrine lesions, the occurrence of this syndrome in association with an ovarian tumor should at once lead to the suspicion of a *granulosa-cell tumor*. This suspicion will usually be proved correct. When curettage in cases of uterine bleeding occurring in women long after the menopause yields a typical endometrial hyperplasia, a granulosa-cell carcinoma should be suspected even if, as in very stout patients, the lesion cannot be felt. If a tumor can be palpated, the suspicion becomes almost a certainty.

During reproductive life the *symptoms* produced by granulosa-cell cancer, aside

from those of ovarian tumors in general, are similar to those characterizing the more common type of hyperestrinism. Menstruation is usually excessive, often irregular, and sometimes normal, and long periods of amenorrhea are not uncommon.

While in most cases the microscopic examination of granulosa-cell cancer can be made from the morphological and growth characteristics of the granulosa cells, many such cancers will be overlooked unless one is familiar with the numerous patterns produced by the connective tissue changes and the apparent intermutability of the epithelial and connective derivatives of the progranulosa ovarian mesenchyme.

*Arrhenoblastoma* should always be suspected when an ovarian tumor is demonstrated in a woman who, previously of the normal feminine type, has exhibited symptoms of defeminization or masculinization.

*Dysgerminoma*, on the other hand, often occurs in sexually subnormal or pseudohermaphroditic persons. As it has nothing to do with the production of manifestations of sexual subnormality or pseudohermaphroditism, the latter do not regress after its removal.

The *Brenner tumor* of the pure or solid type is readily recognizable, but the fact that the same histogenetic factor is concerned in the more and more frequently reported fibroma ovarii adenocysticum and also in at least a small proportion of serous and pseudomucinous cystadenomas must be borne in mind.

The usual block or two made from ovarian tumors for pathological study is often not sufficient for recognition of the nature of the neoplasm. In the study of many tumors, such as those which are discussed in this article, examination of sections from many parts of the growth is always desirable and very often essential for diagnosis.

**KRUKENBERG TUMORS.**—These tumors represent ovarian metastases of epitheliomas of the digestive tract. R. Crousse and A. Dupont (*Bruxelles-méd.* 15:902 (June 16) 1935; 931 (June 23) 1935) report 32 cases, including 9 personal cases; 3 of which are given in detail.

They state that Krukenberg tumors are usually bilateral. As a rule, the tumor on the right side is larger than that on the left. The neoplasms are usually of an elastic consistency and frequently show cystic areas. They are surrounded by a capsule and on section show hard whitish and softer yellow necrotic areas. Krukenberg, who first described these tumors in 1895, regarded them as primary, but subsequent studies have shown them to be secondary to tumors in the digestive tract. In the authors' cases and the other cases tabulated, the primary tumor was in the stomach. While the stomach is its most common site, it may occur also in some other part of the gastrointestinal tract.

Krukenberg tumors occur usually in young women, in the period of full sexual activity. Of the authors' 9 patients, 5 were under 40 years of age.

While in some cases the gastrointestinal cancer is diagnosed and perhaps operated upon and the symptoms of the ovarian tumors develop subsequently, in the majority the first symptoms are due to the ovarian tumors, the digestive symptoms are slight, and the primary tumor is discovered only after a correct diagnosis of the nature of the ovarian tumor has been made. Of the 3 cases reported in detail, the first was of the latter type. In the second, the symptoms of ovarian tumor developed 3 years after gastrectomy. In the third, the ovarian tumors were found at autopsy after a palliative operation for a gastric cancer that had caused symptoms for years.

The *ovarian symptoms* are relatively slight. The most frequent sign is amenorrhea. This is a relatively late sign caused by considerable destruction of the ovarian tissue. Menorrhagia and metorrhagia are rare. Often the first sign noted is enlargement of the abdomen. This is due not only to the growth of the tumors, but also to the concomitant ascites.

*Bimanual examination* discloses usually a bilateral mass which, as a rule, is definitely separated from the uterus. This mass is usually hard and nodular. If its situation in relation to the uterus cannot be definitely determined by bimanual examination, hystero-graphy will show the uterine cavity to be normal.

*Histologically*, ovarian tumors of the Krukenberg type consist of an invasion of the ovarian parenchyma by epithelial cells of two types. In one type the epithelial cells are isolated, smaller than those of the ovarian stroma, but with large nuclei often in active mitosis. These cells often secrete mucus which accumulates within the cell, pushing the protoplasm toward the periphery. In the second type of invasion the cells are not isolated, but grouped in masses, sometimes with irregular glandular cavities, and form more or less typical glandular epithelioma. In this type, the mucus sometimes escapes from the cells, forming plaques in the surrounding connective tissue. The ovarian stroma in contact with the cancer cells reacts by an increase in fibrocytes, which form a structure resembling that of fusocellular sarcoma. It was this characteristic that led Krukenberg to consider these tumors to be of the digestive tract. Of 3 of the authors' cases in which the nature of the primary (gastric) tumor was determined, the examination revealed a diffuse epithelioma in one case, linitis plastica in one, and an atypical glandular epithelioma in the third.

The *prognosis* of Krukenberg tumors of the ovary is definitely poor. At least two-thirds of the patients die within a few months after operation. The diagnosis is usually made late, because symptoms are slight, and when operation is done, only the ovarian tumors are removed, as a rule, the primary tumor being overlooked or considered inoperable. In only a few cases has operation been done on both the ovarian and primary growths at one time or within a short interval. In 2 or 3 of the authors' cases in which gastrectomy was done, the patient was not kept under observation. In 1 case death occurred at the end of 6 months and the ovarian tumors were found at autopsy. One patient returned to the hospital 3 years later with inoperable Krukenberg tumors. The third patient was found to have bilateral ovarian tumors a year after the gastrectomy. The tumors were removed, although large. This patient is living and well 9 months after the operation. None of the authors' cases had radical operations on both the primary and the secondary tumors within a short period. **Gastrectomy** was done first and then **hysterectomy**. Unless such radical operations are possible, cure cannot be expected.

**TRANSPLANTATION.**—B. Solomons (J. Obst. and Gynec. Brit. Emp. 3:487 (June) 1936) reports the case of a married woman, aged 28, who gave a history of *ovaritis* as a complication of mumps and a gynecologic operation in 1930, when an ovarian cyst with the ovary was removed. She was in a highly neurotic condition, had not menstruated for 3 years, and had lost all feeling of sex. Examination at the time (August, 1933) revealed a normal pelvis. She was admitted to the hospital and numerous endocrine products were injected without the desired effect, *i. e.*, to bring about menstruation. On July 21, 1935, the abdomen was opened. A

very small uterus was found. The ovary had apparently been removed on the left side, and the ovary on the right side was slightly cystic and adherent to the broad ligament. The uterus was then split and the endometrium exposed. It was very atrophic in appearance. A piece of endometrium was dissected from a uterus removed for multiple fibroids from a woman of 34 immediately prior to the operation and was grafted into the uterus of the patient by means of fine interrupted catgut sutures. In addition, a piece of ovary which was attached to the removed uterus was placed in the right rectus muscle. On September 25th, two months after the operation, the first menstruation ensued, lasted 3 days and has been regular since.

E. Douay (Mém. Acad. de chir. 62: 439 (Mar. 25) 1936) presents a study of 128 cases in which grafting of autogenous ovarian tissue was done *after hysterectomy* with *oophorectomy* performed at the Broca Hospital in the period from 1929 to 1934.

In all of the cases the graft was taken either during operation from the removed ovary which was placed in a sterile towel or after operation from the ovary which was placed in a sterile dish. In 60 per cent. of the cases in which the graft appeared healthy, the hysterectomy was done for fibroma, cancer, salpingitis, or hematocele. When the ovary was small, it was divided through its greatest diameter to make 2 grafts (68 cases). When it was large, only a part of it was used, each graft representing one-fourth of the gland (9 cases). In 40 per cent. of the cases the grafted ovary was pathological. In 25 cases, it was infected; in 13, sclerocystic; and in 5, sclerotic. In 3 cases there were bilateral ovarian cysts. In 5 cases, tuberculous salpingitis was present, but the ovary was free from manifest tuberculosis. The pathological grafts were

well tolerated. In all cases bilateral grafting was done. In none was a graft expelled. The resistance and vitality of ovarian tissue are remarkable. The activity of the pathological grafts was no less than that of the normal grafts.

The grafting is simple and can be done quickly.

*Technic.*—A 2-cm. incision having been made in the inguinal region, Kocher forceps are introduced through the wound, advanced obliquely downward and inward toward the labium majus to a depth of from 4 to 6 cm., and then opened to create a bed in the tissue to receive the graft. The graft is then introduced to the bottom of the tract with the forceps, its oozing surface posterior. The operation is concluded by the introduction of a suture in the skin. It consumes only a minute.

With the graft in this region, it is quite easy to control its growth and condition and, if necessary, to cut it out. The implantation of a graft from the same ovary on each side increases the chance of success. Often grafts function alternately, one every other month. By the described route of implantation the graft is protected from infection through communication with the operative field.

After the operation the labia swell. A hematoma may form, but is soon resorbed. In cases of *hot, painful swelling*, **moist compresses** will give relief. During the first months following the operation the graft may decrease in size. Castration symptoms develop in 65 per cent. of the cases. The first signs of activity of the graft, *i. e.*, swelling of the graft and sensitivity of the region of implantation, usually appear from 3 to 4 months after the operation. However, in about 8 per cent. of the reviewed cases they appeared the first month and in 2 cases not until the twelfth month. Treatment with extract of the **anterior lobe pituitary gland** or **ovarian extract** will hasten the stage of activity. When 2 grafts have been implanted ac-

tivity is usually bilateral and regularly alternative. Occasionally it is greater on one side than the other. In some cases it may be unilateral and occur every month or every two months. It may be accompanied by transitory swelling. The enlargement persists for from four to seven days and is followed by a period of resorption lasting for a week, the whole process taking from fifteen to twenty days.

As soon as the graft begins to enlarge the castration symptoms begin to subside. In 99 per cent. of the reviewed cases more or less complete hormone equilibrium, and sometimes even hyperfunction, ensued. The improvement in the general condition resulting from such grafting is marked and greater than that obtained by the usual endocrine therapy. The graft must be placed so that it will be protected against pressure from the clothing and will not cause inconvenience in the sitting position or in intercourse. The patient must be informed of the monthly swelling, or operation for a suspected pathological condition may be done.

If the *swelling* is annoying and excessive, **puncture and evacuation of the follicular cyst** will prove beneficial. From 5 to 15 c.c. of fluid may be withdrawn. In 13 per cent. of cases there are periods of hypofunction with corresponding symptoms, and in 12 per cent., periods of hyperfunction. Removal of the graft for excessive swelling produces castration symptoms. In 14 (11 per cent.) of the reviewed cases the grafts atrophied without becoming active. In 14 cases, activity persisted for from 3 to 6 years; in 20, for from 2 to 3 years; in 15, for from 6 months to 2 years; and in 9 for less than 6 months.

The incidence of failure increased with the patient's age. Nevertheless the results were sufficiently encouraging to justify such grafting at the time of the

menopause. Grafts implanted after hysterectomy for fibroma give less favorable results than those implanted following hysterectomy for carcinoma. The transplantation of an infected ovary is associated with little risk of infection. In 70 per cent. of cases *castration symptoms* develop when the grafts cease functioning. **Hormone therapy** will relieve them and may even reactivate the graft. Conservation of the uterus seems to favor vitality of the grafts.

### PELVIC INFLAMMATION.—

**Treatment.**—The treatment of pelvic inflammation by **iontophoresis** of acetyl - beta - methylcholine - chloride (**mecholy**) is discussed by A. Jacoby (Am. J. Obst. and Gynec. 31:93 (Jan.) 1936). Recently a group of drugs has been made available, each of which produces vasodilatation and thus induces hyperemia. Of these acetyl-beta-methylcholine-chloride, the latest compound produced, seems to be the most effective.

When applied locally by iontophoresis, there is some general reaction, but a much more pronounced effect is noted at the site of application. This is particularly true in doses of 0.2 to 0.3 Gm. (3 to 5 grains). When applied to the skin, the drug causes a rise in skin temperature for 2 to 8 hours, marked sweating for 4 to 10 hours, slight redness, a faster rate of capillary flow, and a slight increase in the white blood cell count. The marked vasodilatation is due chiefly to its effect on the arterioles.

The following *technic* is employed:

With the patient in the lithotomy position, a bivalve speculum is inserted and the vaginal vault exposed. All excess of secretion is wiped away. Several thicknesses of gauze 6 inches square are soaked in 20 c.c. (5 drams) of a 1 per cent. solution of acetyl-beta-methylcholine-chloride, prepared by dissolving 1 Gm. (15 grains) of drug in 100 c.c. (3½ ounces) of distilled water. This square of impregnated

gauze is carefully spread out against the entire vault of the vagina. A thin vaginal electrode, with the active end wrapped in gauze and soaked in the 1 per cent. choline solution is placed firmly against the gauze pack. The speculum is withdrawn, leaving the electrode in place. This electrode is attached to the positive pole of a galvanic apparatus. A flat dispersive pad 6 by 8 inches, well moistened in warm water, is placed on the lower abdomen and connected to the negative pole. To insure an even contact, a sandbag is placed over the negative pad and the patient is directed to press it firmly against the skin. The current is turned on gradually until 15 or 20 milliamperes are used, and allowed to flow for 20 to 30 minutes. The current is then slowly shut off and the electrode and vaginal gauze removed. The amount of acetyl-beta-methylcholine-chloride thus introduced has been found to be 31 per cent., or 62 mg. (1 grain). Allowing for the small quantity which adheres to the vaginal wall, this corresponds closely with the estimated amount of 24 per cent., or 48 mg. ( $\frac{3}{4}$  grain), which should theoretically be introduced by this technic. No douches are prescribed at any time. The treatment is repeated every other day. No local reaction is noticed by the patient, but there is usually a generalized sweating, flushing, and sense of warmth, with marked salivation during the treatment. In some instances there is an initial drop of blood-pressure. When the general reaction is too pronounced, the application is interrupted, and 1/150 grain (0.45 mg.) **atropine sulphate** is given hypodermically. This acts as a physiologic antidote and immediately counteracts all untoward symptoms.

Of the 10 patients treated by the iontophoresis of acetyl-beta-methylcholine-chloride, 7 with extensive pelvic inflammation were completely cured. In several, concomitant painful menstruation was relieved. No effect was produced on nabothian follicle cysts, small cystic degeneration of the ovaries, or large ovarian cysts. Further investigations to more completely define the uses and limitations of this treatment are in progress. So far as can be judged from a small number of cases, it is likely that this method of treatment is an effective agent in promoting the rapid absorption of inflammatory pelvic ex-

udates, with incidental relief of symptoms. It produces no change in productive pathologic conditions. It seems to be superior in its effects to other methods of exciting pelvic hyperemia, because it has a much more sustained physiologic action.

**STERILITY.—*Diagnosis.***—Methods in sperm analyses and evaluation of therapeutic procedures are discussed by R. S. Hotchkiss (J. A. M. A. 107: 1849 (Dec. 5) 1936).

The appraisal of the semen constitutes the chief and final index of male fertility, and the clinician must be able to recognize relative degrees of seminal deficiency and learn to correlate these with the clinical data to determine whether the husband is the chief or contributing factor to the barren marriage.

If it is borne in mind that spermatozoa are able to exhibit motility longer in low temperatures than at body heat and that the ingredients of the average condom are hostile to their life, much error and confusion will be avoided by proper instructions relative to the methods of collecting the semen for analysis.

Following a period of 3 days' abstinence, the ejaculation is collected directly into a wide-mouth glass container and allowed to remain at room temperature or lower until delivered, within 1 or 2 hours, to the examiner. An active specimen will exhibit motility for 30 hours or longer under these conditions.

A routine semen analysis should include the following details:

1. The average volume of the ejaculate is from 3 to 4 c.c. Variations from 1 or 2 drops to 10 c.c. are encountered. Specimens of less than 0.5 in amount fail to produce an adequate seminal pool, which ordinarily provides a medium for the survival and protection of the sensitive sperm.



2. The appearance and viscosity of the fresh ejaculate is entirely different from that one-half-hour old. Self liquefaction is then completed, much to the benefit of motility of the sperm. If the eventual motility is of a good grade, it is likely that variations in viscosity have little or no clinical significance.

3. The  $pH$  of a seminal specimen usually falls within the range of from 7.7 to 8.5. If no motility is found, it is of particular importance to obtain a  $pH$  determination, for in rare instances a shift to a low reading of 6.0 and 6.2 has been found to be associated with necropermia.

4. Interval examinations are made to determine the viability of the sperm, which is usually about 24 hours at room temperature.

5. The number of spermatozoa is determined by the use of the usual equipment for counting blood cells. A sodium bicarbonate-phenol solution is used as the diluent; it destroys motility to permit an accurate estimation of the cells present in each cubic centimeter and in the total ejaculate. The average fertile male will produce from 100,000,000 to 150,000,000 spermatozoa per cubic centimeter or from 400,000,000 to 500,000,000 in the total ejaculate. One group of eminent authorities state that in their experience pregnancy does not occur if the cell count is below 60,000,000 per cubic centimeter.

The author believes the more reliable and consistent cell counts have been on the basis of cells present in the total volume of the ejaculate rather than in units of cubic centimeters. The bulk of the semen undoubtedly originates in the prostate and seminal vesicles, and variations in the amounts of these secretions will accordingly dilute or concentrate the specimen. In the former instances an apparent deficiency may be inferred if the cell count is expressed in cubic

centimeters, whereas the number of sperm in the total ejaculate may prove to be normal.

6. The examiner must be familiar with the variations in the morphology of the spermatozoa just as the hematologist is conversant with blood cytology. A stained smear is prepared and the percentage of atypical cells is established by count. If some of the more complicated stains are not available, the Gram stain gives a fair visualization of the cell structure after proper fixation. Moench has evidence that leads him to believe that if more than 20 per cent. of the cells have abnormal form, sterility or miscarriage will result.

**Etiology.**—S. R. Meaker (*Ibid.* 107: 1847 (Dec. 5) 1936) discusses the newer ideas of the gynecologic aspect of human sterility. These new ideas may be reduced to 3 fundamental principles.

First, in the great majority of cases of human infertility the cause of that defect is not some single abnormality, but rather the summation or totality of several factors. Complete diagnostic studies show that the average childless couple presents 4.79 factors, each of which diminishes to some extent their capacity for conception. Factors of absolute sterility, such as closed tubes, are found in only about 30 per cent. of clinical cases. Seventy per cent. of couples who apply for the relief of childlessness show no single condition that would account for their difficulty.

Second, the multiple factors involved are partly *genital* and partly *constitutional*. In Meaker's opinion, the general or constitutional condition is fully as important as the local or genital condition with relation to the fertility of an individual. States of constitutional depression include not only endocrine insufficiencies, but also various non-endocrine conditions, such as chronic intoxication, metabolic disturbances of

extrinsic origin, debility, and general inferiority.

Third, the several factors present in each case are *seldom limited to one partner*. Meaker finds that among the couples who consult him, only about 10 per cent. of the husbands and 5 per cent. of the wives are free from all objectively demonstrable evidence of infertility.

In the female, *genital hypoplasia* is important. Numbers of women possess genital organs scarcely developed beyond that stage of differentiation which would be normal in a 10-year-old girl. Hypoplasia is inimical to fertility in several respects, chiefly as regards immaturity of the ovaries, which ovulate imperfectly if at all.

Second, the endocervical mucus is often so thick and tenacious that spermatozoa are unable to penetrate it. Faults of this sort are demonstrated by postcoital examination, a test which should always be performed, though it never eliminates the need for study of a condom specimen. *Abnormal viscosity of the endocervical secretions* may derive from several causes, among which the commonest are poor drainage, due to a pinhole os externum and endocervical infection. *Faulty sex hygiene*, with resultant chronic passive congestion, is a factor never to be overlooked.

Third, partial or complete *obstruction of the Fallopian tubes* constitutes an obvious impediment to conception. No doubt gonorrhea plays the major rôle in producing this particularly unfortunate factor. Nevertheless, other causes are to be considered: developmental defects, for example, and nonvenereal inflammations.

Fourth, the last, there is the serious matter of *deficient oögenesis*. Not only must the ovary be mechanically free to liberate mature egg cells, but the gland must also be able to create that divine spark, that sum total of hormones, which

will endow the ovum with adequate vitality. Many an ovary is inhibited on purely mechanical grounds when retention cysts or a thick tunica albuginea interferes with the normal maturation and rupture of follicles. It may also happen that Graafian follicles are absent in some generally depressed state, most often in an absence of that stimulation which should normally come to the ovary from the anterior lobe of the pituitary.

The author's clinic has used for 10 years a measurement which is called the *uterine index*. This is an expression of the ratio between the length of the uterine body and the length of the cervix; the relation is 0.25 in infantile cases and 0.75 or more in cases in which normal development has been attained. Figures thus obtained are far more significant than a casual notation of such stigmas as an elongated and anteflexed cervix.

A follicular cycle, Meaker claims, even though abortive, may still produce a certain number of lutein cells. He, therefore, does not accept without some question the conclusions based on endometrial biopsies, however well they appear to indicate successive events in the physiologic program of the ovary.

**Treatment.**—In the gynecologic field, Meaker (*Ibid.*) states that methods of treatment are fairly well standardized. *Endocervical infections* may be cured with the **cautery**, and if a *pinhole os* prevents free drainage of the secretions, a small posterior median **discission** can be done. **Insufflation of gas and injection of iodized oil** relieve many partial *tubal obstructions*; in *fimbriated-end occlusions*, **salpingostomy** is a valuable procedure, provided this is invariably accompanied by postoperative measures that will maintain the established patency. *Deficient oögenesis* calls for the services of the endocrinologist

or of the internist more often than for those of the gynecologist. Conservative *operations on the ovaries*, notably the **resection of retention cysts**, are of great utility for the purpose of restoring normal follicular function. The factor of *hypoplasia* remains exceedingly difficult to manage in the adult patient, in whom all developmental urge or growth impulse has been lost. But there exists in this connection a brilliant opportunity to practice **preventive gynecology**, for it appears that most of such developmental arrests can be foreseen and forestalled by proper attention to the menstrual behavior and to the general health of the adolescent girl.

F. C. van Tongeren (Gynéc. et obst. 33:239 (Mar.) 1936) recommends **sounding of the uterus** for cases in which no absolute cause for the sterility can be demonstrated by pelvic examination. The technic is simple, and, when carried out with precautions for asepsis, without danger. It is contraindicated by symptoms indicative of inflammation, such as pain, an abnormal discharge, and erosin. Bilateral salpingitis, of course, renders it of no avail.

As a result of this treatment, 52.2 per cent. of 67 women who had been sterile for more than 2 years and 35.6 per cent. of 39 with primary sterility became pregnant. Pregnancy took place soon after the treatment. Of the women who had been sterile for more than 2 years, 41.8 per cent., and of those with primary sterility, 23 per cent., became pregnant within 6 months. The described treatment was of value also in sterility associated with retrodisplacement of the uterus. Of 11 women treated unsuccessfully with a pessary to correct the retroversion, 5 became pregnant after sounding of the uterus.

The *most favorable time* for the procedure is about the tenth day of the cycle—before, rather than after, ovula-

tion. At this time the chances are most favorable for immediate results and there is little risk of interrupting an early pregnancy. The author attributes the good results to dilatation of both the external and internal os. Strictures at these points frequently cause sterility, as they prevent adequate uterine drainage (menstrual blood, cervical secretions). Stagnating secretions, such as are present especially in the infantile uterus with an elongated cervix and in certain uteri with retrodisplacement, destroy the spermatozoa.

When sterility persists for more than 6 months after this treatment, sperm examination, salpingography, and transuterine insufflation are advisable. The author emphasizes that too definite conclusions should not be drawn from a single sperm examination, as pregnancy has been known to occur in women whose husbands had been considered sterile because a single semen examination had shown paucity or absence of motile spermatozoa. He believes that **insufflation** and **salpingography** may have a therapeutic effect by breaking down mild tubal adhesions. **Salpingostomy**, **stomatoplasty**, and other **plastic procedures** are occasionally successful.

**STERILIZATION.**—C. B. Lull (Am. J. Obst. and Gynec. 31:101 (Jan.) 1936) reports an analysis of 223 cases of surgical sterilization. Of these patients there were sterilized at Cesarean section, 111 or 0.64 per cent.; at hysterotomy, 19 or 0.11 per cent.; and at gynecologic operation, 93 or 0.54 per cent.

The procedure consists simply in picking up the middle portion of each Fallopian tube, ligating it with an absorbable suture, and then resecting the loop. The importance of using an absorbable suture cannot be stressed too much, because when a silk ligature is

used the chances of fistula formation are unquestionably increased. Practically no bleeding occurs, although when doing this by the vaginal route some tearing of the mesosalpinx may occur and give rise to moderate hemorrhage. Lull has never observed hemorrhage in doing this operation by the abdominal route which required any extensive ligation or resection of the tube. At subsequent laparotomy upon 4 of the patients in this series, it was definitely demonstrated that the cut ends had drawn apart and that the plastic exudate of the peritoneum had become organized in such a manner that it did not seem possible for a fistula to occur. Both ends of the tubes were shrunk up to a very narrow strand. In addition to having the opportunity of studying these cases at subsequent operation, the writer injected lipiodol into the uterine cavity of many of them. In no cases was there any escape of lipiodol from the uterine cavity.

Because of its simplicity and safety, and because there have been no known failures up to the present time, the author feels that it is also a secure operation to perform.

This operation can be done vaginally as well as abdominally.

Five deaths occurred in this series; all were either bad operative risks or death was caused by some of the accidents of postoperative convalescence.

#### UTERINE CERVIX.—INFLAMMATION. — *Treatment.* — C.

D. Hoffmann (J. Florida M. A. 23:81 (Aug.) 1936) states that in any treatment for *chronic cervicitis* with erosion, eversion or laceration, the histopathology of the condition must be borne in mind, *i. e.*, the malarrangement of the columnar and squamous epithelium. Whatever line of treatment is adopted, success will not be reached until the pathologic condition is corrected and the underlying

and superficial tissues are restored to their normal arrangements and cell layers.

Among the plans of treatment are (1) the various chemical applications with or without tamponage, (2) electrical cauterizations, (3) coagulations, (4) radium, (5) surgical and, last but not least, the Crossen conization with the cutting electrode. The author evaluates these different methods and states that at his hospital **conization with the Crossen loop** has been done with good success. The technic is that used in the Hyams loop method but has the distinct advantage over the latter of accomplishing in one revolution what would take many revolutions for the Hyams loop. The operation with the Crossen loop requires less than one minute and gives a cleanly coned out operative field. It is very unusual for any free bleeding to occur and rarely, if ever, are sutures required. If the conization is properly done and the current is not too hot, little scar tissue is encountered. The author dilates the cervix to about twice its size before conization. He feels that in this way the infected tissue is packed together, the extra edema is pushed out of the tissue and there is not the danger of taking out more than the desired amount of normal tissue at the base of the infected tissue. Other advantages of the conization method, besides the assurance of getting the disease tissue and the reduced amount of cicatricial tissue postoperatively, are that it is an ideal method of removing tissue for biopsy, the hospitalization is from 36 to 72 hours, and there is little loss of blood and no shock to the patient.

The author observed more than 200 of these cases all the way from operation through the various stages of healing. Ordinarily the slough has completely gone in from 7 to 10 days, leaving a clean nonirritated cervix. The

cervix at the end of three weeks presents the clean regular appearance of the nulliparous cervix.

L. S. Kritschewsky and E. Werbatus (Monatschr. f. Geburtsh. u. Gynäk. 101: 346 (Mar.) 1936) employ **ammonia silver salt solutions** in the treatment of *endocervicitis* and in *cervical erosions*. They use a 1:20,000 solution in boiled water. Following a preliminary vaginal douche with 1 liter of this solution, the vaginal portion of the cervix is brought down and the external os is wiped with sterile gauze. A long needle is then introduced into the submucous tissue of the cervix and the tissues are infiltrated with 10 c.c. (2½ drams) of the solution. The injection is made in 4 directions (anterior, posterior and both sides) into the submucous tissue of the cervix and partly into the muscular layer. This procedure resulted in considerable infiltration and edema of the cervix. In the course of the injection, some of the fluid escaped through the eroded surface into the cervical canal, which was thus irrigated, but at least 2 or 3 c.c. actually entered the submucous tissue and the muscular layer. In the course of the later injections, when the cervix became softer, the injection was considerably less difficult and from 5 to 6 c.c. of the injection fluid remained in the cervix. The injections were repeated at 5-day intervals, and the total number varied between 2 and 8. The authors obtained favorable results with this treatment in 63 of 66 cases.

L. H. Biskind (Lancet 2: 1049 (Nov. 9) 1935) has previously used **basic phenylmercuric nitrate** in treating 100 cases of specific and nonspecific *endocervicitis* and associated conditions. The results showed an invariably favorable response in all of the conditions encountered, both specific and nonspecific, except when *Trichomonas vaginalis* was the inciting agent. The

character of the infection could be changed often by a single application. When complete and rapid clinical recovery was not attained, there was enough improvement to allow of the successful use of adjuvant treatment. In effective concentrations, both as a local application (1:1250) and as a douche (1:25,000), basic phenylmercuric nitrate was nontoxic and almost nonirritant to the vaginal mucous membrane, and it proved effective in the presence of tissues. When it was used persistently as a douche, the patients did not develop symptoms of mercury poisoning and the output of mercury in the urine was negligible. The author has subsequently used basic phenylmercuric nitrate in 41 cases seen in the dispensary and 22 in private practice. The former comprise 11 cases of vaginitis in children (5 gonorrheal and 6 due to a mixed infection, including 1 due to *Bacillus coli*), 13 cases of *Trichomonas vaginalis* infection in adults 14 cases of endocervicitis (7 gonorrheal and 7 nonspecific), 1 case of rectovaginal fistula, 1 case in which a slough followed vaginal hysterectomy, and 1 case of paracervical sinus with infection following cauterization. The latter group consisted of 11 cases of gonorrheal endocervicitis, 2 of trichomonas infection, 4 of nonspecific vaginitis, 4 of nonspecific endocervicitis, and 1 case of tinea infection involving the perineum and labia.

The method of treatment in the utility of phenylmercuric salts, in particular basic phenylmercuric nitrate, indicate that these compounds combine with the highest bactericidal and fungicidal potency yet discovered for any class of compounds a relatively low toxicity for animals and for man.

**CANCER.—Histological Classification.**—A study was undertaken by H. Chambers (Am. J. Cancer 23:1 (Jan.) (1935) to determine the extent to

which the response of malignant tumors to irradiation varies with their histological structure and whether there is evidence to support the theory that tumors of certain histological types (*e. g.*, adenocarcinoma) are insensitive to irradiation. Of 678 cases of epidermoid cancer of the cervix treated at the Marie Curie Clinic, 228 were discarded as unsuitable. The grading of the remaining 450 cases was based on the extent of differentiation and the degree of cell activity, but the general structure of the growth was also considered. The author grades squamous-cell cancers as follows:

Grade 1: All typical squamous carcinomas of the adult common type. (Incidence, 15 per cent.)

Grade 2: Tumors composed of thin spindle cells resembling those of the basal germinating layer. (Incidence, 9 per cent.)

Grade 3: All tumors in which there is a distinct tendency to form stratified epithelium. (Incidence, 54 per cent.) These tumors are subdivided into keratinized, differentiated, transitional, and anaplastic growths.

Grade 4: Anaplastic growths which show no formation of stratified epithelium. (Incidence, 22 per cent.) These tumors are subdivided into: (*a*) those arranged in alveolar masses with a fair amount of intervening tissue, and (*b*) those composed of a solid mass of cells with little intervening tissue which in some respects resemble sarcoma.

The age incidence of the tumors of the various histological grades is about the same except that there is some indication that the anaplastic growths (tumors of Grade 4) are more common in younger than in older women.

The duration of symptoms seems to have no relation to the clinical stage of the disease (League of Nations classification). In many of the most advanced cases among those reviewed, the symptoms had been present for less than 2 months and in some of the less advanced cases they were of the longest duration.

The clinical varieties of local growth, *viz.*, nodular, infiltrating, ulcerating, crater-forming, fungating, cauliflower, endocervical, and pyometric, were studied. The cauliflower growths were chiefly of Grades 3 and 4b, but every histological type was represented in each clinical variety.

The irradiation treatment used at the Marie Curie Clinic is a modification of Forssell's method. In general, the principles of therapy have not been modified since the Clinic was opened in 1925. Radium has not been used interstitially and supplementary deep x-ray therapy has not been employed. The chief object of the treatment has been the direct application of a dose of irradiation large enough to cause the malignant cells to disappear without producing irreparable damage to normal structures. It is, in fact, a surface treatment to the uterine cavity and the vaginal vault. In no way has the dosage been influenced or altered by the histological character of the growth. Although this method succeeds in treating carcinoma cells close to the surface, it fails to destroy or seriously alter the growth of cancer cells situated more deeply or metastases in the pelvic glands. Therefore, the results are dependent upon the clinical stage of the disease when the treatment is begun and disappearance of the local growth is of more value in determining the effect on the cancer tissue than is the patient's ultimate condition.

The author reviews the results of treatment not only in the 450 cases of *squamous-cell cancer* which were graded, but also in 50 cases of *adenocarcinoma* of the cervix. Of 90 patients in clinical Stages 1 and 2 (League of Nations classification), 80 (89 per cent.) have been apparently free of local disease for 2 years or longer since the institution of the treatment. Of those in clinical Stages 3 and 4, 144 (63 per cent.) are

locally cured. There is comparatively little difference between the various histological grades. However, the best results were obtained in cases of transitional cancers of Grade 3, in which the incidence of local cure was 74 per cent., and cases of adenocarcinoma, in which the incidence of local cure was 73 per cent.

The author believes that the treatment used at the Marie Curie Clinic will cure the great majority of growths limited to the cervix (Stage 1), irrespective of their histological type. When the more advanced cases—for example those of Stage 3—are considered separately, a difference of not more than 15 per cent. is found between the various histological types so far as local cure or the number of 3-year survivals is concerned. This is true also when the results in the entire series are considered. Moreover, it is quite evident that adenocarcinoma are not insensitive to irradiation.

**Diagnosis.**—A. Bucher (Schweiz. Med. Wchnschr. 66: 30 (Jan. 11) 1936) points out that the appearance of a vaginal discharge that has a reddish tint, the intermediate hemorrhages, or hemorrhages occurring after examination, after coitus or after forced defecation are late symptoms; they indicate the terminal stage. Pain also is a late symptom, for by the time pain is felt the carcinoma has already spread to the pelvic connective tissue, the peritoneum, the sheath of the psoas and the ischiadic plexus. Carcinoma of the uterine cervix does not produce subjective symptoms during the early stage. He believes that the early diagnosis of carcinoma of the uterine cervix is possible only if every woman beyond the age of 30 is subjected once a year to a thorough examination. The usual methods of examination are bimanual palpation and examination with the speculum. Palpa-

tion is the more valuable of these two methods, because the wall of infiltration surrounding the carcinoma can better be felt than seen. If it cannot be decided whether an area is carcinomatous or not, an exploratory excision is advisable, but is justified only if there is reason to suspect the presence of carcinoma.

The author admits that for the practitioner it is extremely difficult to recognize the nature of changes in the uterine cervix merely by means of palpation and by inspection with the eye. A reliable serologic diagnosis would be of great help, but although there are some promising methods, none have as yet produced satisfactory practical results. For this reason hope lies chiefly in the improvement of the local methods of examination and in this connection the author mentions *Schiller's iodine test* and *colposcopy*, which should be used together. Colposcopy is the stereoscopic observation of the cervix with centered illumination and considerable magnification. Colposcopy reveals that the cervical carcinoma does not necessarily appear in the form of nodules, but rather in the form of peculiar epithelial changes. Hinselmann designates these stages as matrix regions. They appear as leukoplakia as well as under other forms. Later examination often reveals leukoplakia where previously other changes had existed. Histologic studies indicate the uniformity of the various changes, in that they reveal atypical epithelium with a tendency to cornification and to growth into the connective tissue and into the glands.

Approximately 20 per cent. of the so-called matrix regions prove to be carcinomas. They are the symptomless incipient stages and their recognition by colposcopy demonstrates the great value of this diagnostic method. The *matrix regions* are removed by **shallow amputation of the cervix**. Thus cure is

affected without great surgical risk and without danger of relapse. Moreover, the uterus retains its functional capacity (menstruation and eventually pregnancy).

The necessity of *colposcopy* in the early diagnosis of carcinoma of the cervix is stressed by Hinselmann (Wien. klin. Wchnschr. 48:1478 (Nov. 29) 1935), who deplores that it is rarely done in a satisfactory manner and that because of this the results have been negligible. To be sure, a careful colposcopic technic is not enough, clinical experience and a thorough histologic knowledge being indispensable for the proper estimation of the observations. In discussing the cell material of cervical carcinoma, the author stresses the importance of the atypical epithelium in the cervical mucous membrane, which is capable of forming horny tissue. He shows that there are two methods for the recognition of the atypical epithelium on the cervix: (1) the *Schiller's method of iodization*; (2) the *optic method*, which is a further development of the examination with the speculum. He emphasizes that with the colposcope it is possible to recognize the atypical epithelium not only after cornification has taken place, but also when only a few parakeratotic layers cover it, when only the superficial cells are slightly flattened, and even in the absence of these changes. He shows that colposcopy and the iodine test are not meant to replace each other, but should be combined. As far as the differentiation of the atypical epithelium is concerned, colposcopy is superior to the iodine test; nevertheless, in doubtful cases the author has resorted to it and would not like to dispense with it. He demonstrates the importance of colposcopy for the early diagnosis of cervical carcinoma with a case history.

W. Schiller (Lancet 1:1228 (May 30) 1936) warns that the aqueous iodine

test is not specific for carcinoma but marks off only the areas that do not contain glycogen. Glycogen is always absent in cancer, but not only in cancer. It is absent also in carcinomatous transformation of epithelium, hyperkeratosis of the squamous epithelium of the cervix, keratinization developing in prolapse, which may also cause the glycogen to disappear, and when the superficial layers of glycogen containing epithelium have been rubbed off by inflammation, maceration or the examining finger or speculum. Thus, there are different possibilities which cause the epithelium of the surface to remain white.

The method of iodine painting is easily carried out in an outpatient department, requiring no special training for the doctor and causing the patient no pain. A further field of application for iodine painting is in the revelation of cancerous marginal zones of progressed carcinomas. The method can be applied without difficulty, but it has its full value only when carried out on as many patients as possible. The author has seen patients 25 or 26 years of age with smooth, homogenous shining white portios that seemed altogether above suspicion to the eye of the clinician but when painted with iodine showed a small white speck, which proved to be a carcinoma when scraped off. The gynecologist who paints only the suggestive cases is sure to miss the most important stage—the smallest, clinically latent cancer. The more general the examination by iodine painting, the smaller will be the proportion of positive cases.

In the author's last series, about 20 of every 100 women examined in the outpatient department showed suspicious areas, and of these 20, only 1 or 2 proved to be cancers upon histologic examination of the scrapings. But even if only 1 per cent. of the women examined give a positive diagnosis, the



result is still exceedingly satisfactory, for carcinoma when detected and treated at that early stage gives nearly 100 per cent. security for definite permanent healing. If it were possible by this procedure to examine systematically at intervals of a few months as large a number of women as possible, a predominant proportion of cervical cancers might be obtained for treatment at such stages as would fully guarantee permanent healing. Thus it would be possible to lower greatly the mortality of this disease.

**Treatment.**—The difficulties that are encountered in the course of radium treatment of tumors in the small pelvis induced F. Daels (*Zentralbl. f. Gynäk.* 60:306 (Feb. 8) 1936) to resort to the **exteriorization** of the small pelvis. To do this, he makes a transverse incision into the abdominal wall, 1 cm. above the pubic symphysis and above Poupart's ligament, then ligates the epigastric vessels, sutures the lower edge of the peritoneum to the skin above the symphysis and the inguinal canal, severs the peritoneum of the posterior half of the pelvic inlet up to the pelvic mesocolon, sutures the upper edge of this line of incision to the parietal peritoneum of the anterior abdominal wall, sutures the lower edge to the skin and thus forms a new diaphragm at the level of the promontory.

He found it advisable to wait from 3 to 6 days after the exteriorization before beginning the **radium** treatment. Then the radium tubes can be introduced without difficulty to the right and left of Douglas' pouch and to the right and left of the vesicouterine fold. In the beginning, the author alternated between periods of treatment and periods without treatment (4 or 5 days in length), but later he found that the treatment could be continued uninterruptedly for from 10 to 18 days. He stresses as the *ad-*

*vantages* of the method the possibility of uniform irradiation of the small pelvis; the prevention of injuries to the connective tissue; the possibility of prolonged, weak irradiations; the absence of retention of infected secretions from the cancerous focus, which frequently occurs in the case of intrauterine or intravaginal irradiation; and, finally, the possibility of careful control.

V. Bonney (*Am. J. Obst. and Gynec.* 30:815 (Dec.) 1935) has performed 483 **Wertheim operations**. Except in the cases of women who were very old or the subjects of advanced cardiac, pulmonary, renal, or other disease, he operated whenever there was any chance of completing the operation. This principle has had the disadvantage of raising both the operative mortality and the incidence of recurrence. On the other hand, it has saved lives which otherwise would have been lost. Bonney presents results which he believes represent the limit to which surgery alone can go in the treatment of carcinoma of the cervix. He has not employed preoperative irradiation, but a few of his earlier cases were referred to him as having been "rendered operable" by radium. The operations were exceedingly difficult, and none of the patients survived 5 years. Bonney has used postoperative irradiation only in cases in which it was impossible to remove carcinomatous glands from the iliac vessels. In no case did the patient survive 5 years.

If the patients who cannot be traced and those who died of other disease within 5 years after the operation are reckoned as having died of recurrence, the incidence of freedom from recurrence for 5 years after operation was 24.6 per cent. If these patients are excluded from the calculation, this percentage is 25.6. With regard to the incidence of freedom from recurrence for 10 years, the figures may be expressed briefly by saying that

on the 5-year basis the operation cures 2 of every 5 patients operated upon and 1 of every 4 patients seen; while on the 10-year basis, it cures 1 of every 3 patients operated upon and 1 of every 5 patients seen.

In the reviewed cases the incidence of operability was 63 per cent. Therefore 37 per cent. of the cases remained to be treated by irradiation. Five of the 37 patients, *i. e.*, 5 per cent. of the 100 originally seen, may be dismissed from consideration as beyond the reach of any measure. Of the 32 remaining, a 5-year cure can be obtained by irradiation in a certain proportion. According to radiological statistics, this is about 5 and this number must be added to the number of 5-year cures obtained by operation.

*Subtotal versus Total Hysterectomy.*—Attention is called by J. V. Meigs (Am. J. Obst. and Gynec. 31:358 (Feb.) 1936) to the large percentage of nulliparas developing cancer of the retained cervix, the high incidence of fibroids in the series of cases reviewed, and the very low incidence of cancer of the retained cervix, as compared with the incidence of such cancer suggested by the literature of today.

Conservative surgery should be the rule, and the life of the patient the most important consideration. There is no doubt, that total hysterectomy is a more formidable and more serious operation than simple subtotal removal of the uterus. The morbidity, the chance of injuring the ureters and bladder, the possibility of vaginal prolapse, and the foreshortening of the vagina in the young married woman all are against the routine performance of this operation.

The proper procedure in cases in which hysterectomy is required is careful inspection of the cervix with the patient in the lithotomy position, followed by curettage of at least the endocervix in the young and of the whole

uterus in the old. If the cervix looks suspicious, it should be repaired or amputated, or a biopsy should be done, and no further operation should be performed until a frozen section has been made. If a pathologist is not available for the examination of a frozen section, it is better to wait 3 or 4 days for a laboratory report regarding the presence or absence of cancer. The curettings should, of course, be subjected to examination. If cancer is present, total abdominal or hysterectomy or radium irradiation, should be done. If cancer is not present subtotal removal of the uterus may be performed with assurance that it is the best procedure.

A diseased cervix should never be left untreated. It should be repaired or removed by amputation or total hysterectomy. Cauterization may be relied upon if it can be done thoroughly and deeply enough.

The author does not advise the routine performance of total hysterectomy, but advocates this operation for cases in which repair or amputation is difficult and cauterization is out of the question. He says that the performance or non-performance of a total hysterectomy must depend upon the judgment of the surgeon and his study of the individual case. No dogmatic rules can be laid down. Too much criticism of subtotal hysterectomy and too much enthusiasm for the total operation will of necessity cause an increasing mortality and morbidity.

*TREATMENT OF PAIN.*—*Intraspinal Alcohol Injections.*—Practically all of the women with Group III and Group IV carcinoma of the cervix develop severe pain in the lower abdomen, lower back, or down the legs. The pain is due to involvement of the sensory nerves in the malignant process, and at present there are 3 means of combating this pain other than direct treatment of the malig-

nancy. The first consists of the use of derivatives of opium, chiefly **morphine**, and is the method employed almost universally by most physicians. However, morphine is not entirely satisfactory because as the patient's tolerance for the drug increases, larger doses must be given; some women cannot take the drug because it produces nausea and vomiting, others become morphine addicts and are difficult to handle, and the drug becomes increasingly more expensive for poor patients. The second method is surgical and consists of **pelvic sympathectomy** and **chordotomy**. While the former operation is relatively simple, it requires an abdominal operation and, as shown by J. P. Greenhill and H. E. Schmitz (Am. J. Obst. and Gynec. 31:290 (Feb.) 1936), it does not relieve all patients. Chordotomy is a serious operation which must be carried out by a skillful neurosurgeon. The third means of overcoming the pain due to a malignant growth consists of **blocking the nerves** which conduct the sensation of pain by means of various solutions. The authors have used **alcohol** for this purpose and have injected it into the spinal column.

Since the nerve fibers of the superior hypogastric plexus are sensory and not motor, resection of the superior hypogastric plexus above the hypogastric ganglion will relieve most if not all the pain which arises in the pelvic organs. Subarachnoid alcohol injections are effective in relieving pain because they injure the peripheral nerve fibers in the posterior or sensory roots.

The authors performed a **pelvic sympathectomy** upon all patients with advanced carcinoma who had severe pain, and observed complete relief from pain in 37.5 per cent. of their first 40 cases, partial relief in 35 per cent. and failures in 27.5 per cent. However, when they selected only those patients who had pain

in the middle of the lower abdomen, pain low in the back, rectal tenesmus, bladder pain, and pain associated with vesicovaginal and rectovaginal fistulas,, they relieved practically all of them completely.

More recently they have resorted to **intraplasmic injections of alcohol** to relieve the pain associated with Group III and especially Group IV carcinoma of the cervix. Among their first 40 patients taken at random, they have been able to obtain complete relief in 85 per cent., partial relief in 5 per cent., and no beneficial effect in 10 per cent. In some cases relief has lasted for 8½ months. The only patients not suitable for intraspinal alcohol injections (at least in the lumbar region) are those who have pain not only in the kidney region but also in the parametrium, due to stricture of the ureter associated with hydroureter and hydronephrosis.

They believe that intraspinal injection of alcohol is preferable to sympathectomy not only because it is much simpler and can be performed by any qualified physician familiar with the essential features of this procedure, but also because it may be used in a greater number of cases and it gives relief to a larger percentage of women with advanced carcinoma of the cervix.

Greenhill and Schmitz (*Ibid.*) then describe the *technic* of pelvic sympathectomy in detail. Since many patients who should be subjected to this type of operation are poor surgical risks, it is best to open the abdomen under direct **infiltration anesthesia**. This is a very simple procedure and requires only a few minutes. The rest of the operation may readily be performed under a short **ethylene** or **ether anesthesia** or even under **infiltration anesthesia**.

The patient should be placed in the Trendelenburg position after a midline incision has been made from the umbilicus downward toward the pubis for about 10 to 12 cm. After the peritoneal cavity is opened, the small intestines are packed off and the sigmoid and rectum are pushed to the left side and held

there with a wide retractor. The uterus, adnexa, and bladder may then readily be inspected and palpated to determine the extent of the malignant infiltration. A complication such as pus tubes may also be detected which can be remedied by a surgical procedure. The region of the lower two lumbar vertebrae and the upper part of the sacrum is exposed to view.

In thin women, it is possible in some cases to see the presacral nerve immediately beneath the peritoneum. Whether or not the nerve is seen, the parietal peritoneum above and in the middle of the sacral promontory is elevated and incised with scissors. This incision is extended upward for about 4 or 5 cm. and for a similar distance down along the sacrum. When the peritoneal flaps are pulled aside, a fibrocellular connective tissue layer will be exposed covered by more or less adipose tissue. This tissue can easily be separated from the peritoneum and the lower end of the aorta without danger. It is in this layer that the presacral nerve lies. With an aneurism needle the tissue is elevated at the bifurcation of the aorta and the dissection is carried to a still higher level. As this is done, it will be found that in most instances the tissue spreads out in a triangular manner. The middle sacral artery should be pushed away from the nerve, but if it is injured, it can readily be ligated.

After the dissection is carried as high as it is desirable to go, the layer of nerve tissue is separated from the underlying tissue down past the sacral promontory into the pelvic cavity. In this region the plexus has divided into the two hypogastric nerves, hence it is necessary to dissect one of these nerves at a time. At least 2 or 3 cm. of each hypogastric nerve should be resected in addition to 4 cm. or more of the superior hypogastric and the intermesenteric plexus. The fibrous tissue layer which contains the hypogastric nerves is much more resistant than that which contains the presacral nerve. As the dissection is carried out, nerve filaments projecting outward will be encountered. These should be followed as far laterally as possible before cutting them. In most instances ganglia will be included in the resection. The dissected tissue should preferably be removed in one piece.

It is not necessary or advisable to ligate the presacral nerve or the hypogastric nerves before cutting them, because the only blood vessels in intimate contact with them are insignificant vasa nervosum. In fact, Cotte is of the opinion that ligatures may be the origin

of secondary pains. Very rarely is bleeding encountered which requires more than simple temporary pressure to check it. (Where the mesosigmoid is very short, care must be exercised to avoid injury to the inferior mesenteric vessels.)

After the nerve is resected, the posterior parietal peritoneum is sutured with plain catgut and the abdominal wall is closed in the customary way. Since women with inoperable carcinoma are usually cachectic and prone to exhibit poor wound healing, it is advisable to use silkworm gut or other permanent suture material to aid in the closure of the abdominal wall.

*Technic of Intraspinal (Subarachnoid) Injection of Alcohol.*—No preliminary medication is given since the immediate effects of the injection are to be observed. Most patients with advanced carcinoma of the cervix and other genital organs have much more pain on one side than on the other. The patient is placed on the side opposite to that where most of the pain is present. A pillow or pad is placed under her pelvis and side to elevate the sacral and lumbar portions of the spine, her back is arched as much as possible, her body turned somewhat ventrally, and the head lowered slightly. By placing the patient in this attitude, the sacrolumbar region of the spine is raised to the highest level and at the same time the posterior or sensory nerve roots are made to lie horizontally. The anterior or motor nerve roots come to lie in a plane which is usually out of reach of the alcohol. Even if the motor nerves are not removed from the field of the alcohol, as occurs in the cauda equina, they are not often affected, because sensory nerves are more susceptible than motor fibers to the effects of alcohol.

Some one should hold the patient in the proper position. A weak solution of iodine or other antiseptic is applied over the lumbar and upper sacral regions. In most of the early cases the fourth lumbar interspace was selected for the injection of the alcohol. Many injections were made in the first, second, and third lumbar interspaces to see if the pain which some women develop high up in the abdomen and back could be relieved. Since this could not be accomplished in all cases and since the high injections sometimes failed to relieve all the pain in the lower abdomen and back, Greenhill and Schmitz (*Ibid.*) are now again making all of their injections in the fourth lumbar interspace. An ordinary lumbar puncture needle with a stylet is used. The needle is injected into the desired interspace just as

for an ordinary lumbar puncture, and the writers prefer not to use novocaine in the skin before inserting the needle. After the needle is in the subarachnoid space, as evidenced by the flow of spinal fluid, 0.5 c.c. (8 minims) of absolute or 95 per cent. alcohol is injected into the cerebrospinal fluid. For this purpose it is best to use a tuberculin syringe so as to be sure not more than 0.5 c.c. is injected. Furthermore, the alcohol must be injected very slowly, drop by drop, taking about 2 minutes for the injection of the 0.5 c.c. This will avoid a mixture of the alcohol with the spinal fluid. The alcohol rises immediately to surround the posterior roots, because the specific gravity of alcohol is about 0.806, whereas that of the spinal fluid is 1.007. No attempt should be made to draw spinal fluid into the syringe to mix it with the alcohol, because this is exactly what is not wanted. After the injection is made, the needle is withdrawn and the puncture hole covered with sterile gauze and adhesive.

Before the injection is completed, the patient will complain that the upper leg feels numb and hot and that she cannot move the leg. The numbness is almost routinely experienced after the injection, but disappears spontaneously after a few hours or few days in most of the cases. In spite of what the patient says concerning her inability to move the leg, she can easily move it when requested to do so. At the same time that the patient informs the authors of the numbness she also often tells them either voluntarily or in answer to their query that her pain has disappeared. The longer the patient is permitted to lie on her side, the better the results. Hence, the operators now keep their patients on their side for 2 hours after the injection. Then these women are permitted to get up and walk around. Some find difficulty in getting up from their chair because their "leg is asleep." Sometimes the leg feels heavy and the patient experiences some trouble in walking up steps because the knee flexes readily. These sensations usually wear off in a few hours, although in some women they last a number of weeks. Nearly all of their patients who were ambulatory went home within 3 hours after the injection, and no ill effects have been observed from this procedure. It is perhaps best, however, to keep the patient in a hospital for 24 hours.

If the patient has pain on both sides, an injection is made a week later with the patient lying on the opposite side. The same amount of alcohol is injected.

Until a few months ago they restricted the subarachnoid injection of alcohol to patients with hopelessly advanced *cancer*. They did this because they feared the effects of absolute and 95 per cent. alcohol on the spinal cord. Since they have observed no bad effects from the injections, they injected alcohol intraspinally in 6 women who had severe *pruritis vulvæ* and/or *pruritis ani* and obtained striking relief, thus far up to 4 months.

W. Wayne Babcock, of Philadelphia, in discussion stated that the technic of alcohol injection may not be quite as simple for every one as it is in the hands of those who are unusually expert. With a very stout patient, it may be necessary to introduce the needle a distance of 3 or more inches before it reaches the spinal canal. In such a case particularly, it is difficult to tell just where the needle will hit the dura. The dura may be entered on the left side, the right side, or in the midline. If the dependent side of the cord is entered, the nerve roots opposite those it intended to block may first be affected. Again, it is not always known to what depth the point of the needle has entered the spinal canal; as the distance between the anterior and posterior roots is not great, the needle may pass beyond the posterior roots and deposit the alcohol about the anterior roots. Thus for accurate localization, gravity, as influenced by the position of the patient, largely must be depended upon. Despite these possible errors, however, it must be conceded that the results reported have been surprisingly good.

It is evident that the concentration and dose of alcohol used is very important. From the injection of 1 c.c. (16 minims) Babcock obtained a persistent motor weakness of the leg. While the patient had relief from pain, she would not permit an injection on the other side for fear she would not be able to walk.

In general, the anterior roots seem to be very much more resistant to the action of drugs than the posterior ones. For the posterior roots of a dog, a **novocaine solution** of the strength of 0.5 per cent. suffices to produce a sensory block; for the anterior roots 5 times this concentration is required in order to produce a motor block. Thus, it may be possible to use larger quantities of weaker solutions of alcohol, perhaps even about the cervical cord, and have motion preserved, although sensation is lost. The lower percentages of alcohol seem to be quite safe. In Babcock's clinic they have probably given for spinal anesthesia over 35,000 injections of anesthetic solutions containing from 10 to 13 per cent. of ethyl alcohol, and in no case have they seen any paralysis or sensory loss from such use of alcohol. From injections of solution contaminated with 10 per cent. of methyl alcohol, 2 patients had rather prolonged retention of urine, and a persistent weakness of the sphincters. One patient also had weakness of the perineal muscles.

**CANCER OF CERVICAL STUMP.**—The subject of stump carcinoma of the cervix is of interest because it is always felt that when a carcinoma occurs in the cervical stump, primary removal of the cervix would have prevented such a catastrophe. The removal of the cervix would have been preventive, but if the cervix is perfectly normal on examination, there is no necessity for the removal. Of the 544 patients who had supravaginal hysterectomies at the Jefferson Medical College Gynecological division, L. C. Scheffey (J. A. M. A. 107:837 (Sept. 12) 1936) found carcinoma of the cervical stump to have developed in 5, an incidence of 0.902 per cent.

In 3 patients carcinoma was probably present and overlooked at operation; in 2 patients this was possibly true. The

condition was observed in all 5 from 6 to 21 years afterward.

The incidence of carcinoma of the cervical stump does not justify complete hysterectomy as a routine procedure in every case.

Careful preliminary inspection, biopsy of the cervix, and diagnostic curettage will reduce to a minimum the chance of overlooking carcinoma.

A diseased cervix always requires treatment, but when **cauterization** will suffice, its practice as a preliminary to supravaginal hysterectomy makes complete removal unnecessary. In a few instances, **trachelectomy** or **trachelorrhaphy** may be preferable to cauterization. From this review it would seem evident that those patients who did receive preliminary cervical treatment were less prone to develop carcinoma of the cervical stump.

**UTERUS.—DIAGNOSTIC PROCEDURES.—Hysteroscopy.**—In recent years hysteroscopy has again aroused the interest of investigators with the result that this method of visualizing the uterine cavity has been perfected to a point where it gives promise, after still greater improvements have been made, of becoming a most important diagnostic procedure for every gynecologist. A. Hamant and E. Durand (Rev. franc de gynéc. et d'obst. 31:1 (Jan.) 1936) describe the hysteroscope devised by Segond and their *technic* of its use in the study of the endometrium.

After antiseptic preparation of the vulva and vagina and dilatation of the cervix with Hegar bougies under local or general anesthesia, the hysteroscope is introduced into the uterus and the uterine cavity irrigated with sterile water until the return flow is entirely colorless. The optical attachment is then inserted and to make visual inspection possible the uterine cavity is distended with

sterile water. To prevent the water from flowing back through the cervix, care is taken to limit the preliminary dilatation of the cervix to that which will hold the hysteroscope tube in tight approximation with the cervical canal. The amount of pressure necessary to distend the uterine cavity (650 mm. water or from 25 to 30 mm. Hg.) is not great enough to cause the water to flow through the tubes into the peritoneal cavity. In none of the authors' cases has the water passed through the tubes during hysteroscopy.

Hysteroscopy is *contraindicated* in fixed retrodisplacements of the uterus, pregnancy, periuterine inflammations, and profuse metrorrhagia.

The chief difficulty in hysteroscopy is not the technic but the interpretation of the images. The authors present 22 illustrations in color to show their findings in normal and pathological conditions. For the removal of sections of endometrium for microscopic examination they use a special biopsy attachment. In their studies of removed uteri they have compared the findings of hysteroscopy with the macroscopic appearance of the opened uterine cavity. They believe that catheterization of the fallopian tubes and direct treatment of intra-uterine lesions will be possible when suitable instruments are devised.

**HEMORRHAGE.—Types.**—Five clinical types of *functional uterine bleeding* are considered by L. Wilson and R. Kurzrok (Am. J. Obst. and Gynec. 31: 911 (June) 1936).

1. *Puberty Bleeding.*—This may begin with the very first period or may follow one or more apparently normal periods. In their experience, the follicular hormone content of the urine is usually low and occasionally no hormone is found in a 24-hour specimen. They have never found it to exceed the normal 10 to 20 rat units per liter.

2. *Maturity Bleeding.*—In the majority of instances, the onset follows a pregnancy, whether full term, a miscarriage, or an ectopic.

3. *Preclimacteric Bleeding.*—A similar type of functional bleeding very often occurs in women approaching the menopause and may be accompanied by the characteristic vasomotor symptoms of this period.

4. *Ovulation Bleeding.*—In some women, whose periods are otherwise normal, there may occur at the time corresponding to ovulation, a variable amount of uterine hemorrhage. Usually it does not amount to more than a bloody vaginal discharge of a few hours' to 2 or 3 days' duration. Occasionally, however, it is as long and profuse as the regular menstrual flow from which it is clinically indistinguishable.

5. *Cyclical (Anovulatory) Bleeding.*—This type of bleeding is associated with sterility, first, because the failure of ovulation prevents the liberation of a mature ovum, and second, because the absence of the corpus luteum prevents the conversion of the proliferative endometrium into a pregravid (secretory) type.

**Pathology.**—A survey of Wilson and Kurzrok's (*Ibid.*) material consisting of over 600 specimens from cases of functional menstrual disorders reveals that there are basically only 4 types of endometrium: proliferative, transitional secretory, and menstrual. The normal endometrium goes through the complete ovulatory cycle. The transitional endometrium reflects the changes during ovulation and represents the transformation from the proliferative to the secretory phase. Failure of ovulation results in the persistence of the proliferative phase. If the action of the follicular hormone is prolonged and unopposed by progesterone, cystic and glandular hyperplasia of the endometrium results. The

latter is thus only an exaggerated form of a proliferative endometrium.

There is no single type of endometrium constantly associated with either functional bleeding or amenorrhea.

The persistence of cystic and glandular hyperplasia of the endometrium long after the bleeding has been completely stopped by pregnancy urine or anterior pituitary extract definitely indicates that the cause of the bleeding must be sought for in some extraendometrial factor.

The authors believe that bleeding *per se* is due to a special hormone elaborated by the anterior lobe of the hypophysis.

This bleeding hormone is separate and distinct from the follicle-stimulating and luteinizing hormones.

It is not gonadotropic, but acts directly on the endometrium.

Its production is stimulated by the follicular hormone.

Its activity is inhibited but not destroyed by progestin.

The actual onset of bleeding occurs when a certain concentration of bleeding hormone has been reached, provided its action is not inhibited by corpus luteum hormone.

The bleeding stops when the bleeding hormone is exhausted.

**Treatment.**—Excessive functional bleeding may be controlled in any of the following ways, according to Wilson and Kurzrok (*Ibid.*):

1. *Removal of Bleeding Surface.*—Curettage affords only a temporary control of the bleeding. In preclimacteric cases it should be employed routinely as a diagnostic measure, in order to definitely exclude malignancy. In puberty bleeding, curettage should be limited, because it is usually unnecessary and often produces an unpleasant psychic effect on the patient.

2. *Removal of Stimulus (Follicular Hormone) Which Produces Bleeding Hormone.*—The stimulus for the secre-

tion of the bleeding hormone may be removed by **castration**, either by **operation** or **radiation**. The latter is ideal for cases of preclimacteric bleeding, but should never be used in younger women, because it might result in permanent castration.

3. *Prevention of Bleeding Hormone Production.*—This may be accomplished by x-ray irradiation of the pituitary gland, but the authors fear it is too dangerous a method. The exact effect of a given dosage of radiation on an individual patient is not accurately predictable and permanent damage may result when only temporary suspension of function is intended.

4. *Inhibition of Activity of Bleeding Hormone.*—This offers the best method at the present time of controlling functional uterine bleeding. The activity of the bleeding hormone may be effectively checked by the administration of **extracts of the corpus luteum, pregnancy urine** or the **anterior lobe of the hypophysis**. Potent corpus luteum, extracts are not generally available because of their expense and limited supply. Adequate amounts of synthetic **progestin** should soon become available.

Practically every case of functional uterine bleeding can be controlled by **pregnancy urine extract**, provided the dosage is adequate. The average daily dose required during the stage of active bleeding is from 200 to 500 R. U. In very severe cases as much as 750 R. U. daily, in 2 or 3 divided doses, may be necessary. The injections are best given intramuscularly in the buttocks. When the bleeding ceases, the patient may be carried along on much smaller doses (200 R. U. once or twice a week) and this should be continued for several weeks or months.

The authors believe that pregnancy urine extract acts directly on the anterior



pituitary and causes an inhibition of the bleeding hormone.

Certain adjuvants to the treatment of functional uterine bleeding are important. The *anemia* resulting from prolonged or excessive bleeding demands careful attention. In the milder cases, iron may be given. The severe cases often require one or more **blood transfusions**. If a pregnant donor can be obtained, not only are erythrocytes and hemoglobin supplied but also the anterior pituitary-like hormones. Oxytocics as **pituitrin** and **ergot** are occasionally of value, especially when the bleeding is associated with uterine atony.

C. C. Norris and C. A. Behney (Am. J. Obst. and Gynec. 32:661 (Oct.) 1936) report the result of a study made of all patients with *benign uterine hemorrhage* treated with intrauterine **radium** irradiation in the Gynecologic Division of the Hospital of the University of Pennsylvania from 1916 to 1935 inclusive.

The *indications* for radium irradiation in the class of cases under discussion have changed but little since 1916, although dosage and filtrations have undergone modifications. The indications for radium therapy for benign hemorrhage are: patients suffering from pathologic bleeding in whom more conservative measures have failed, who are at or near the menopause, and in whom other pelvic complications are absent; in the myoma group, patients having tumors not larger than a 4 months' pregnancy.

*Contraindications*.—The contraindications to irradiation are:

1. When doubt exists as to the accuracy of the diagnosis.
2. The presence of intraperitoneal lesions other than those responsible for the bleeding and which require surgical intervention.
3. Rapid growth in the case of a supposed uterine myoma.
4. Associated fundal carcinoma.

5. Pressure symptoms.
6. Softening or other evidence of degeneration.
7. Inflammatory lesions within the pelvis, especially those of the adnexa.
8. The presence of neoplasms larger than a 4 months' pregnancy.
9. Submucous tumors, especially if they are pedunculated.
10. Myomas in young women.
11. Anemia markedly out of proportion to the bleeding.
12. Obstructing tumors or malformations that prevent the proper application of the radium.
13. Radiophobia.
14. The presence of cervical myomas.
15. Pregnancy.
16. Highly nervous women.
17. Previous pelvic operations.
18. Painful myomas.
19. Myomas after the menopause.

The destructive effects of irradiation, while being the direct means by which the hemorrhage is checked, also constitute a definite drawback to this form of treatment.

*Results*.—In a study of 1437 cases of benign hemorrhage treated by means of intrauterine radium irradiation, 750 were cases of functional hemorrhage, and 687 of myomas. Of the entire series 1006 patients were followed up for 2 years or more, and 300 of these patients have been observed over a period varying from 10 to 20 years.

Menopausal symptoms occurred in 59 per cent. of 967 reported cases of functional hemorrhage and myomas.

Satisfactory results were secured in 83 per cent. of the group of cases.

The myoma cases yielded about the same proportion of satisfactory results as did those of functional hemorrhage.

Three per cent. developed relapses or complications requiring treatment 10 or more years after irradiation.

The proportion of cases in the followed-up group in which carcinoma of the genital tract developed after irradiation was 1.09 per cent.

The mortality in the entire group was 4 patients or 0.278 per cent.

It is now routine with the authors to attempt **conservative treatment**, which includes **endocrine therapy**, in all women suffering from functional uterine hemorrhage who are in the child-bearing age. Irradiation is advised only after these methods have failed.

**CARCINOMA.**—W. T. Murphy (Radiology 26:178 (Feb.) 1936) reviews 197 cases of cancer of the uterine corpus which were admitted to the State Institute for the Study of Malignant Diseases at Buffalo, New York. The cancers are divided into 6 pathological types based on cellular differentiation. Mentioned in order of ascending malignancy, the types described are: Adenoma malignum I, 9 cases; adenoma malignum II, 76 cases; adenocarcinoma A, 75 cases; adenocarcinoma B, 20 cases; diffuse anaplastic carcinoma, 15 cases; and adeno-acanthoma, 2 cases. Photomicrographs of each type are presented. The classification is similar to that of Healy and Cutler.

The average age of the patients was 58.8 years. The most constant complaints were bleeding (94.4 per cent. of the cases), a discharge (42.1 per cent.), and pain (28.4 per cent.). Backache and urinary complaints were frequent in all types of cases. The difference in the figures for the various types are not striking. The author points out that the incidence of bleeding decreases, and that of other discharge increases, the more highly differentiated the cancer. Pain could not be correlated with the extent or the curability of the disease. The duration of the symptoms was long, ranging in the different types of cases from 1.1 year to 2.3 years. The extremes were 2 weeks and 18 years. The duration of the symptoms could not be correlated with curability. Analysis of data on marriage, pregnancy, and the meno-

pause revealed more evidence of functional deficiency in the cases of anaplastic cancer.

Of the patients who were not operated upon, 82.9 per cent. had enlargement of the uterus at the time of their admission to the Institute. There was no correlation of this enlargement with the pathological type of lesion. Extrauterine masses interpreted as metastases were found in 29.9 per cent. Their incidence decreased with increasing differentiation.

All of the patients were treated by irradiation with the **x-rays** or **radium** or both. Sixty-two had had a hysterectomy elsewhere—17 a panhysterectomy and 45 a supravaginal hysterectomy. For the x-ray irradiation, a 200-kv. machine was used. The radium irradiation was given with a pack as well as by intracavitary and interstitial application. Details of the amounts and screening are reported, but no attempt is made to correlate the results with the type of lesion or the dose of irradiation.

In the 108 cases traced at the end of 5 years, the incidence of apparent cure was 25 per cent. and the incidence of survival with or without disease 35.1 per cent. In the cases in which operation was not performed, the incidence of 5-year cure was 27.2 per cent., and in those treated surgically it was 19.3 per cent. The cases of 5-year cure are analyzed in detail. Although the attempt is made throughout to compare the results in the cases operated upon with those in the cases not operated upon, the material does not permit a fair comparison of the results of irradiation with those of operation. However, it shows that the results are better the more highly differentiated the lesion.

Murphy concludes that functional abnormality of the reproductive apparatus existed in many of the reviewed cases; that *curettage* should always be performed to determine the histological type

of the lesion; and that the treatment should always include **irradiation**. If **hysterectomy** is performed, it should be **total** and confined to the *adenoma malignum* types.

**Treatment.**—*Radium.*—The method discussed by J. Heyman (Wien. klin. Wchnschr. 48:129 (Feb. 1) 1935), which has been described frequently, is a fractional contact treatment in which several irradiations are given in a period of a month. The procedure varies somewhat according to the case. The following is an example of the procedure: 40 mg. of radium are placed in the uterus for 20 hours, 800 mg.-hrs. being thereby given. At the same time 75 mg. are placed in the vagina for 20 hours, 1500 mg.-hrs.—being given. This treatment is repeated after a week and again after an interval of 3 weeks, with the same dosage. Therefore, in a period of 4 weeks, 2400 mg.-hrs. are given in the uterus and 4500 mg.-hrs., in the vagina, a total of 6900 mg.-hrs.

The radium is enclosed in gold or platinum tubes with walls equivalent to 1 mm. of lead, and the tubes are placed in applicators with walls equivalent to 2 mm. of lead. The filtration is therefore 3 mm. of lead. The shape and distribution of the applicators vary in different cases. The relatively strong irradiation of the vagina is given for the purpose of influencing the parametric tissues. The bladder tolerates high dosages of radium irradiation better than the rectum. Therefore, the radium is introduced as high as possible with the aid of tampons.

No difference is made in the dosage in the treatment of histologically different types of cancer. For several years an additional x-ray irradiation with relatively very small dosage has been given, but has proved of little value.

It appears to the author that better results are obtained from the use of

the "radium cannon," *i. e.*, large amounts of radium (formerly 2000 mg. now 5000 mg.) at a distance of 5 cm. from the skin.

Under such treatment the skin of the abdomen and back receives a total of from 25 to 30 Gm.-hrs. and the skin of the vulva, 20 Gm.-hrs. in a few days. Especially in superficially growing carcinomas of the vagina and vulva the author has observed good results from this method. Parametric recurrences do not respond to any type of treatment.

Carcinoma of the body of the uterus is now treated by packing the entire uterine cavity with a large number of small radium preparations. The amount of radium employed ranges from 80 to 200 mg., and the dose, divided into 2 treatments, from 2600 to 4000 mg.-hrs. In addition, because of the danger of vaginal metastases in carcinoma of the body of the uterus a vaginal dose is given. If the condition subsequently becomes worse, total hysterectomy is done. The most common complications are irritations of the rectum. In from 1 to 2 per cent. of the cases death results from sepsis or embolism.

In the period from 1914 to 1928, 1567 cases of carcinoma of the cervix were observed. Thirty of the patients were treated elsewhere. Of the remaining 1537 patients, 327 (21.3 per cent.) remained free from symptoms after 5 years. These represent the absolute cures. Eighty patients were not treated and 2 were subjected to operation subsequently. Of the remaining 1455 patients, 327 (22.5 per cent.) were free from symptoms after 5 years. These represent the relative cures.

Only 56 cases of carcinoma of the body of the uterus were seen; 21 were not treated and 35 were treated by irradiation. Nine of the patients treated by irradiation remained free from symptoms after 5 years. Attention is called

to the great difficulty in the histological diagnosis of carcinoma of the body of the uterus. Specimens presented to the greatest authorities are often very differently diagnosed.

In conclusion, the author states that it is surprising that even in such extensive and homogeneous material, statistics show marked differences in the incidence of cure, for which no explanation can be found. In Sweden the material has improved, as operation is now seldom performed and even favorable cases are treated by irradiation.

nephritis or evidence of myocardial weakness contraindicating extensive operative procedure.

The *prerequisites* for the operation are as follows: The sexual life of the patient should no longer be of importance and the consent of the husband should be obtained. The cervix, corpus, and adnexa should be free from pathology. All cases should be curetted prior to the operation and phenol cauterization of the uterine cavity should be carried out. Erosions of the cervix and vaginitis should be eliminated by suita-

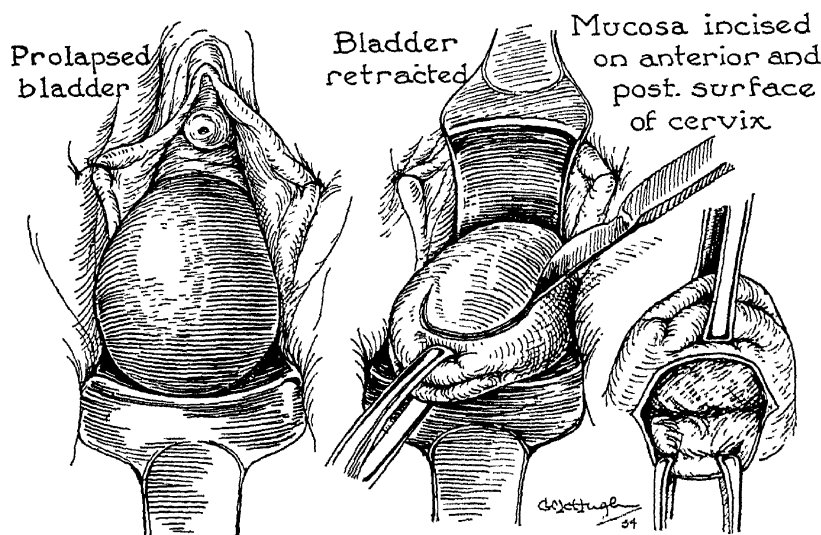


Fig. 1.

(Adair and DaSef: Am. J. Obst. and Gynec.)

### PROLAPSE OF UTERUS.—

**Treatment.**—The Le Fort colpocleisis, an operation consisting of a medical obliteration of the vagina, is employed in special cases of partial or complete prolapse in older women and is discussed by F. L. Adair and L. DaSef (Am. J. Obst. and Gynec. 32: 218 (Aug.) 1936). The operation is applicable to a difficult group of cases, and the results have been very satisfactory.

It is a relatively simple surgical procedure. It is admirably suited to elderly women and may be used when more extensive operations are contraindicated because of obesity, hypertension, chronic

ble treatment. The prolapse should be capable of reduction.

It was found that the addition of a perineorrhaphy added greatly to the results if a relaxed pelvic floor were present. Application of the vesicovaginal fascia in cases with large cystocele also greatly improved the result of operation.

The *technic* of the operation is described by the authors as follows:

The patient is placed in the lithotomy position and the usual perineal and vaginal preparations, catheterization and draping completed. Either local **anesthesia** (0.5 per cent. solution of novocaine) or light **ethylene anesthesia** is used. The cervix is grasped in the midline

and drawn downward with a single-toothed tenaculum forceps.

The first step in the Le Fort colpocleisis is beginning the denudation of the anterior vaginal wall by a snowshoe-shaped incision of

The bladder wall is exposed mesially, close to the cervix, and is pushed upward on the uterus. The fascia is split in the midline and is then sutured to the uterus underneath the bladder wall, as in a cystocele operation.

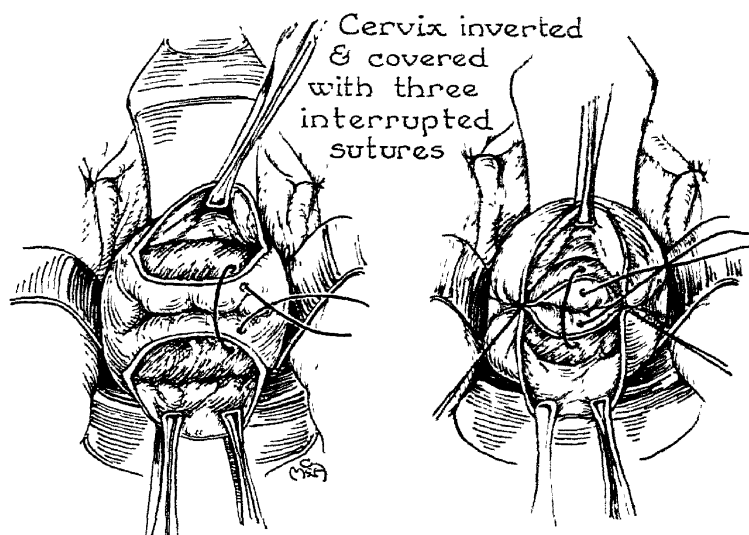


Fig. 2.

(Adair and DaSef: Am. J. Obst. and Gynec.)

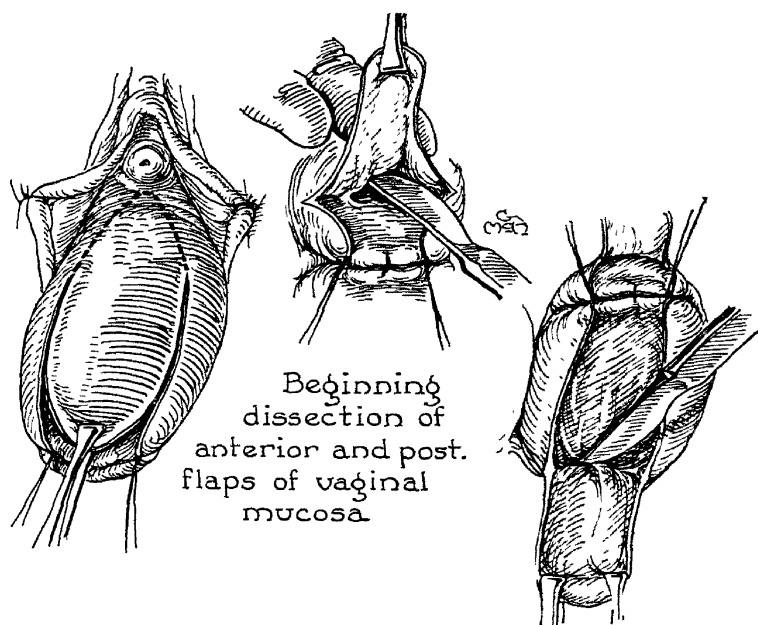


Fig. 3.

(Adair and DaSef: Am. J. Obst. and Gynec.)

approximately 4 by 8 cm. The base of the incision is just above the bladder reflection. The vaginal flap is dissected free downward to the fascial layer and extended toward the urethra for a distance sufficient to expose the vesicovaginal fascia.

The cervix is drawn forward and a similar flap of mucosa is freed posteriorly.

A transverse strip of vaginal mucosa about 2 cm. wide is thus left across each of the lips of the cervix. The margins of these anterior and posterior strips are sutured to one another

with interrupted sutures, thus making a transverse channel below the level of the internal os. These interrupted sutures are inserted so that they enter and emerge on the vaginal surface and the knots, when tied, lie within the vaginal channels.

The lateral margins of the vaginal mucosal flaps are sutured by interrupted sutures anteriorly and posteriorly. These sutures are inserted and tied with the knots inside the lateral channels, as described above. As the margins are sutured downward, the uterus recedes up-

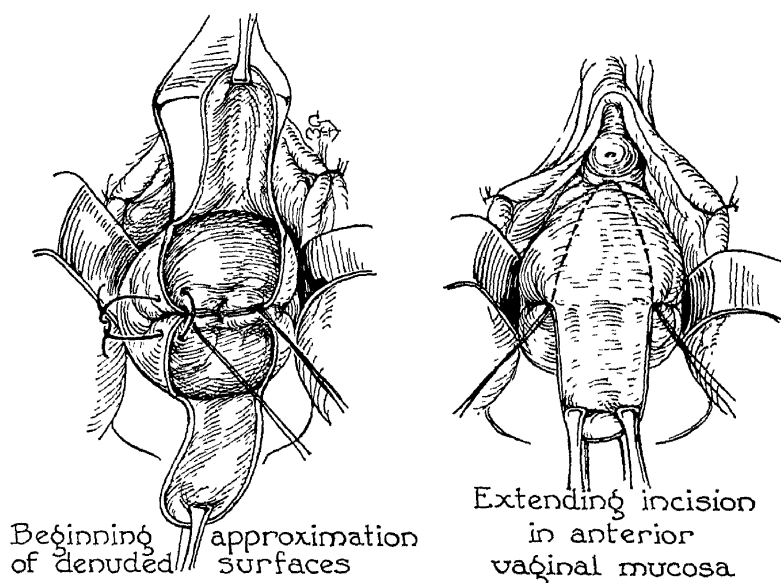


Fig. 4.

(Adair and DaSef: Am. J. Obst. and Gynec.)

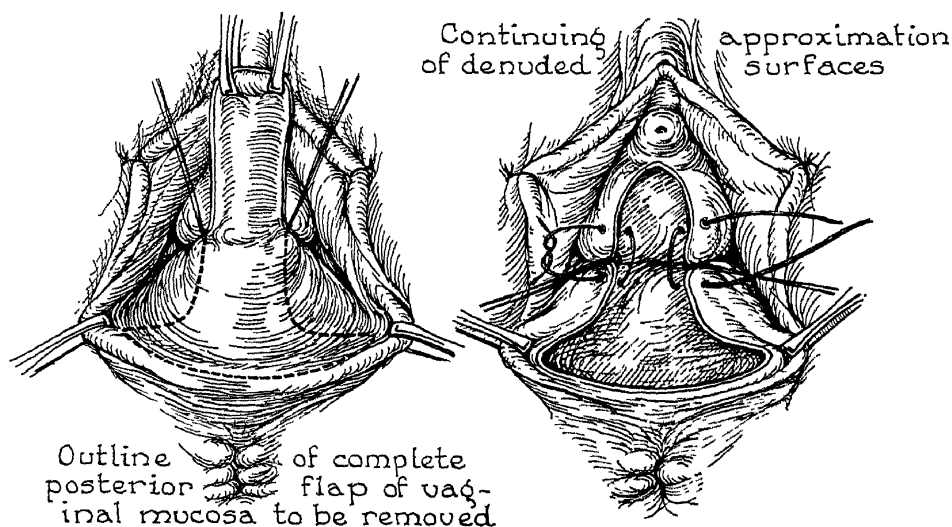


Fig. 5.

(Adair and DaSef. Am. J. Obst. and Gynec.)

The lateral strips of vaginal mucosa are about 1.5 to 2 cm. wide, extending from the transverse cervical strip superiorly to a point about 1 to 1.5 cm. above the external urethral meatus and inferiorly to fuse with the perineorrhaphy incision.

ward and gradually right and left channels about 0.5 in diameter are formed which ultimately extend from the cervix downward to the introitus.

The operation is completed by a typical perineorrhaphy.

The lateral and transverse channels make an inverted U-shaped channel. The lateral channel of one side runs upward from the introitus to the cervix, passes across below the external

os to connect with the lateral channel of the opposite side which extends downward to the introitus. The lateral channels can easily be demonstrated by the insertion of a uterine sound.

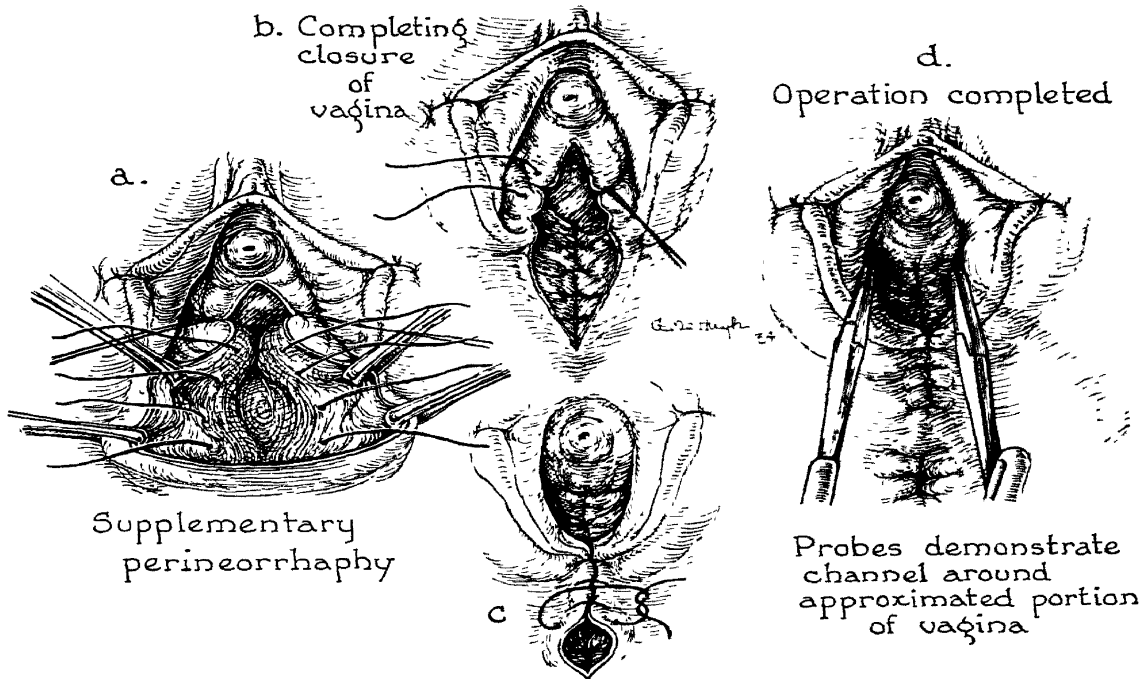


Fig. 6.  
(Adair and DaSef: Am. J. Obst. and Gynec.)

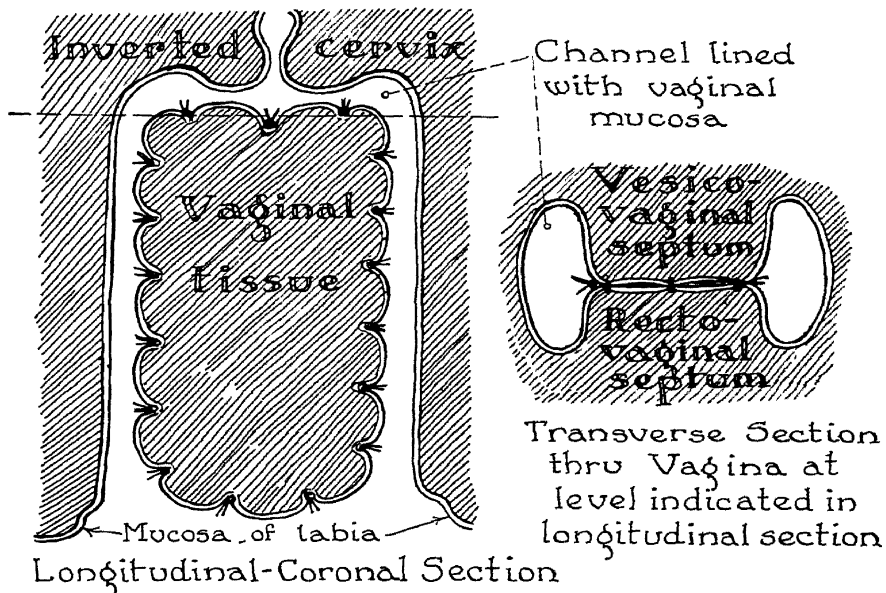


Fig. 7.  
(Adair and DaSef: Am. J. Obst. and Gynec.)

*Convalescence.*—The patient is usually awake before leaving the operating room. The light anesthesia required generally reduces postoperative nausea to a minimum. Patients are kept comfortable with small doses of **morphine sulphate** and placed on **liquids** and a **light diet**. They are encouraged to move about. Recovery is surprisingly rapid. In 7 cases there were mild febrile reactions. Three developed a postoperative cystitis, and 2 had a slight discharge from the operative area. Three patients had prolonged hospital stays of 17 and 19 days. The remainder were up and about on the ninth and tenth postoperative days and left the hospital on the twelfth or fourteenth postoperative day. There were 2 fatalities in the series, a mortality of 5.26 per cent.

On the eighth postoperative day one patient developed a *coronary thrombosis* which was followed by auricular fibrillation. A *popliteal embolism* occurred, with resulting *gangrene* of the left leg; and on the thirty-ninth postoperative day the patient died from hypostatic pneumonia. The second fatality was due to *pulmonary embolism* in a patient who had slight postoperative fever. The embolus occurred after the patient had been allowed up on her thirteenth postoperative day.

In this series the follow-up of the survivors ranges from 3 months to over 3 years. To date there has been one *recurrence*. The uterus prolapsed through one of the lateral channels 3 months after operation. This was corrected by a secondary operation. In all of the other cases the functional results have thus far been excellent.

The *causes for recurrence* of the prolapse have been almost universally the same: (1) Failure to make the lateral channel small enough to prevent recurrence of the prolapse through the side canal; and (2) failure of the sutures to

hold, with resulting partial separation of approximated surfaces.

There has been one *major objection* to the operation: The performance of colposclerosis precludes any further examination of the cervix.

**VAGINITIS.** — *Treatment.* — The glycogenic content of the vaginal epithelium is an important factor in its restoration in the treatment of vaginitis due to trichomoniasis, mycosis or senility, according to F. L. Adair and H. C. Hesseltine (Am. J. Obst. and Gynec. 32:1 (July) 1936). They believe that **hormonal therapy** is effective because it stimulates the production and deposition of glycogen in those tissues.

It is also their opinion that the artificial introduction of substances such as **lactose** into the vaginal canal may supply the vaginal flora with essential pabulum, thus protecting the glycogenic content of the epithelial cells and furthering their normal growth. It is also possible that the cells may absorb some of this material directly from the vaginal lumen. The presence of this chemical in the vagina also favors the growth of the vaginal bacillus which persists in a medium with a pH as low as 3.5.

The reparative process consists essentially in the restoration of a more nearly normal vaginal flora and pH with a gradual change in epithelial growth which results in a normal epithelial layer. The inflammatory reaction subsides and the leukocytes disappear.

They have observed that the epithelial reactions, the cellular growth, and the deposition of glycogen seem to be almost the same in cases of senile vaginitis treated by hormonal therapy and in those which have been treated by the intra-vaginal administration of lactose, 95 per cent., and citric acid, 5 per cent.

The therapeutic principle of creating conditions favoring normal tissue



growth is, in their opinion, much more important biologically than any attempt to destroy pathogenic organisms by antiseptic or other agents.

The normal pH of the vaginal content ranges from 6.0 to 7.0 in childhood, to 5.5 to 6.5 after the menopause, and 4.0 to 4.5 in the intermenstrual period. The acidity is caused primarily by lactic acid. A small amount of this acid may be liberated by the action of enzymes and by glycolysis of the carbohydrates, but the amounts found, especially during the childbearing period, are produced by the action of the vaginal bacilli upon the carbohydrate substance present in the vagina and vaginal walls.

It is interesting to note that *vaginal trichomonads* are not found in the presence of a normal bacterial and cellular flora. The acidity of the vagina is distinctly less in this disease, usually varying from pH 5.0 to 6.5.

The specific etiologic agent of *senile vaginitis* is unknown, but inasmuch as the clinical entity is associated with an abnormal flora, bacteria are almost certainly the cause.

Yeast-like fungi (*monilia* and *cryptococcus*) are established as pathologic agents in vaginal mycoses. These organisms ferment glucose, levulose, maltose, and mannose regularly and often galactose and sucrose, but they do not ferment lactose. In the presence of yeast cells a mycosis may be produced or made worse by the use of glucose.

The above evidence indicates that if conditions favoring the growth of the vaginal bacilli and the production of a greater vaginal acidity are created, trichomoniasis, senile vaginitis, and perhaps some other infections may be treated successfully.

In bacterial infections the epithelial cells and their glycogen-like content need stimulation and perhaps protection. The substituting of a carbohydrate lactose

which the vaginal bacillus can utilize and yet which does not favor the growth of a mycotic organism was tried by these investigators.

Lactose was selected, as it can be utilized directly by the vaginal bacillus, while glucose may be formed by the breaking down of the polysaccharides, which might favor a mycosis.

In the *treatment*, a mixture of **lactose** (95 per cent.) and **citric acid** (5 per cent.) was used for office treatment. Tablets of 2 Gm. (30 grains) amounts for daily home treatment were made from a preparation containing 1 pound of starch paste to 1 gallon of this mixture.

The patient has 1 to 2 heaping teaspoonfuls (3 to 6 Gm.— $\frac{3}{4}$  to  $1\frac{1}{2}$  drams) of lactose (95 per cent.) and citric acid (5 per cent.) placed in the vagina after the diagnosis of *trichomoniasis* or *senile vaginitis* is established. The patient is instructed to place two 2 Gm. (30 grains) pills of this material in the vagina each evening upon retiring. Usually she is instructed to return in 1 week for reëxamination and thereafter the intervals vary from 2 to 3 weeks, depending upon the response to treatment. Infections of the cervix and other sites are treated by appropriate means simultaneously with the carbohydrate therapy.

The patients are instructed to use *no douches*. Occasionally the material tends to accumulate, as the condition improves, and in these instances a plain water douche may infrequently be employed. During menstruation all treatment is discontinued. Sexual abstinence is urged, particularly during the acute stage, but when it is indulged in, condoms are recommended, to avoid spreading the disease as well as to obviate reinfection.

Of 77 patients with *trichomoniasis* treated in this manner, 5 pregnant and 32 nonpregnant women have been

"cured" of trichomoniasis, while 7 and 33, respectively, have improved. In the *senile vaginitis* group 2 have been "cured" and 3 "improved" of a total of 5 patients.

The periods of treatment are rather long. Prompt and immediate cures are uncommon. The maximum period of treatment and observation was 10 months in one instance, while the minimum was 2 months.

#### GONORRHEAL VAGINITIS.—

**Treatment.**—R. M. Lewis and E. L. Adler (J. A. M. A. 106:2054 (June 13) 1936) discuss the results of treatment of gonorrheal vaginitis, with different preparations and amounts of **estrogenic substance**.

In treating gonorrheal vaginitis, estrogenic substance in ethylene glycol given *hypodermically* was relatively effective when used in large doses: 2400 international units daily; 800 international units daily proved disappointing.

The use of vaginal estrogenic *suppositories* (originally 600 international units and later 1000) proved very effective.

Clinical improvement, cessation or great diminution of discharge, is nearly always noted after from 14 to 18 days of treatment.

The administration of estrogenic substance changes the reaction of the vaginal secretions from neutral or alkaline to acid. This, the authors believe, is the major factor in eliminating the gonococcal infection.

The acidity of the vaginal secretions is easily measured and provides a sure guide by which it can be determined whether or not dosage is adequate.

Of 33 consecutive cases of gonorrheal vaginitis in children treated with estrogenic suppositories, 30 yielded negative smears in an average of 20.7 days. Two required 12 weeks of treatment. Five cases are listed as recurrences.

No ill effects were encountered. The authors believe that this method of treatment is safe and harmless, and consider the use of vaginal estrogenic suppositories the most effective method known for the treatment of gonorrheal vaginitis in children.

From their observations in 17 cases of gonorrheal vaginitis in children, L. E. Goldberg, C. L. Minier and E. L. Smith (J. Pediat. 7:401 (Sept.) 1935) are of the opinion that short or long duration of the disease prior to the administration of **amniotin** is not a factor in effecting a cure. The results from the oral method do not differ materially from those by hypodermic injections. The former method would appear to be preferable because of the natural disinclination of a child to be pierced by a needle and also because of the slight danger of an associated abscess, which occurred in one of their cases. The time limit, which is an important factor in therapy, is unquestionably much shortened in effecting cures by amniotin as compared with that by the old methods. Protracted treatment is a disadvantage in any disease, particularly in pediatric practice. The recurrences after this kind of treatment are in all probability much less than with any other type of therapy. The success of the **estrogenic treatment**, in their opinion, depends on the conversion of the epithelial lining of the vagina from an immature type of childhood to an adult type, as demonstrated by Lewis. They are in accord with Huberman and Israeloff, who believe that the acquired layer of cornified epithelial cells acts as a protective barrier against the rapidly multiplying gonococci, thus preventing reinfection. The infecting organisms that were already lodged in the subepithelial spaces have been destroyed.

No ill effects and no definite change in the genitals or in the mammary glands

were observed in any of these children given estrogenic substance, despite the large dosage that was sometimes necessary. Possibly, injurious effects may be delayed in appearing. The last biopsies taken revealed a decided retrogression in the epithelial layers from the adult type back toward the immature type of the vaginal epithelial tissue of childhood. In a subsequent series the authors observed enlargement of the breasts in 5 of 11 cases under treatment with amniotin.

### TRICHOMONAS VAGINITIS.

—E. Allen (Am. J. Surg. 33:523 (Sept.) 1936) maintains that high dry magnification of the fresh, unstained vaginal secretion under reduced illumination simplifies the diagnosis of *Trichomonas vaginalis* vaginitis. Later staining of the dried secretion will serve to differentiate the other common forms of vaginal infection, such as yeast and gonorrhea. The profuse bubbly discharge found in this condition is laden also with various strains of streptococci. These streptococci may invade the urinary tract, Bartholin glands, and probably the deeper structures of the pelvis. In like manner, the male urinary tract may become infected during coitus either with the coccoid organisms or the motile flagellates themselves, and a troublesome urethritis or prostatitis is the result. Constant reinfection renders permanent cure impossible until the male focus has been treated.

**Treatment.**—Permanent cure of trichomonas vaginitis will depend on recognition of possible avenues of infection. Elevation of the general resistance of the patient is important in the therapy. Scrubbing of the vaginal walls should not be instituted until some of the acute reaction has subsided. The vaginal walls are then sprayed uniformly with the powder proposed by Gellhorn (2 parts of acetarsone to 7 parts each

of kaolin and sodium bicarbonate). The introduction of the powder can be accomplished readily by the use of the small blower used for insect powders. The excess powder may be kept in the vagina by inserting a pledget of cotton between the blades. The external genitalia also should be dusted with the powder. This treatment should be done daily for at least 6 days and should be reinstituted for a few days following the next menstrual period. In the interim the patient is instructed to insert into the vagina nightly a vaginal suppository containing 1 per cent. of trinitrophenol, followed in the morning by a 2-quart warm-water douche to which has been added 1 teaspoonful of lactic acid. The frequency of these topical applications should be decreased as the vaginitis improves, but they should be persisted in for at least 3 months. If the symptoms do not disappear rapidly or at any time the patient complains of vulvar irritation, the treatment is changed. A tablet containing the same ingredients as the powder may be substituted for the suppositories. Carbar-sone may be substituted for the acetarsone in either the powder or the tablets. Tampons soaked in the broth filtrate as described by Hibbert may be substituted for the insufflations of powder. A 10 per cent. solution of strong protein silver introduced into the vagina with the patient in the knee-chest position will often produce gratifying results.

The treatment of trichomonas vaginitis by drying plus antiseptics has largely replaced the use of liquid antiseptics, according to P. B. Bland and A. E. Rakoff (Am. J. Obst. and Gynec. 32:835 (Nov.) 1936).

The technic for the dry antiseptic treatment consists generally of a preliminary washing of the vagina and external genitalia by some mild liquid

antiseptic or cleansing agent, drying, followed by the application of the active drug in the form of a powder, tablet, paste or ointment.

A total of 135 patients in attendance at the antenatal and postnatal clinics of the Department of Obstetrics, Jefferson Medical College Hospital, Philadelphia, were treated for trichomonas vaginitis. Ninety-six were pregnant women in the first, second, or early weeks of the third trimester of gestation, while 39 were nongravid cases. The patients selected exhibited clinical and microscopic evidence of infestation with *Trichomonas vaginalis*.

One hundred women were treated with **aldarsone**, 25 received treatment with **acetarzone**, while in 10 patients used as control subjects, kaolin alone was used.

The following *technic* was employed in the treatment of these women:

With the patient in the lithotomy position, the vagina was exposed with a bivalve speculum and the mucosa thoroughly washed with a diluted tincture of green soap and water. The vaginal membrane was then thoroughly dried with cotton pledgets.

The vaginal portion of the cervix was painted with **tincture of metaphen**, and a number of applicators dipped in the solution were successively carried deep into the cervical canal.

The introitus and vulva were thoroughly scrubbed with tincture of green soap and water, and then dried.

The urethra and paraurethral recesses were treated with an aqueous **solution of metaphen 1:500**, repeatedly applied on cotton applicators.

The antiseptic powder preparation was insufflated into the vagina with a powder blower. One-half gram ( $7\frac{1}{2}$  grains) of the arsenical with finely divided kaolin sufficient to make 3 Gm. (45 grains) was used for each treatment. A number of vaginal insufflators were successfully used, including the Gellhorn powder blower, the Powdex insufflator, the Shelanski insufflator, and several designed by G. W. Raiziss.

The patient was treated in this manner on 3 consecutive days. Three additional treat-

ments were given at 3-day intervals. The patient was instructed not to douche and to refrain from intercourse during the period of treatment.

A microscopic research for trichomonads was made before each treatment and at regular intervals thereafter. Smears from the vagina and cervix were taken to note changes in the bacterial flora.

More recently, at the suggestion of T. L. Montgomery, the authors have used a current of warm air from a modified hair drier with much satisfaction.

Laboratory and clinical investigations were conducted to determine the efficacy of a new soluble pentavalent arsenical, **aldarsone** (sodium-methylene-sulphon-amino-hydroxy-phenyl-arsenate) in the treatment of trichomonas vaginitis.

Studies *in vitro* indicated that aldarsone has a definite trichomonadocidal power, which is many times that of acetarzone, and which was not inhibited by human blood serum.

One hundred women with trichomonas vaginitis were treated by the insufflation of 0.5 Gm. ( $7\frac{1}{2}$  grains) of **aldarsone**, **diluted with kaolin**, following **preliminary cleansing** of the vagina and vulva with a **diluted tincture of green soap and water**, instillation of **tincture of metaphen** into the cervix, and an aqueous **solution of metaphen 1:500** into the urethra. A total of 91 women remained free from trichomonas during a period of 3 to 9 months following treatment. Of these 84 women who remained negative after a series of 6 treatments, 5 required an additional series of 6 treatments, and 2 were cured after 2 additional series of treatments.

Of 25 women treated by a similar technic with **acetarzone**, only 12 or 44.4 per cent. remained free from trichomonas, while 13 had repeated recurrences.

It is concluded that clinical experience as well as laboratory studies indicate that aldarsone is much superior to

acetarzone in the treatment of trichomonas vaginitis.

Approximately three-fourths of the women treated were gravid. The results of treatment among the pregnant group with both acetarzone and aldarzone were slightly better than among the nongravid group.

Among a total of 36 recurrences which were noted following treatment with aldarzone, 22 were detected during the first 2 weeks following treatment, while none were noted either clinically or by microscopic study after 8 weeks.

**VULVA.—CANCER.—Treatment.**—The outcome of 74 cases of leukoplakic vulvitis and 112 cases of carcinoma of the vulva seen during the past 30 years is discussed by F. J. Taussig (Am. J. Obst. and Gynec. 31: 746 (May) 1936.)

Previous to 1915 only a few cases came to the writer's notice and all of these were given only palliative treatment. During the past 20 years, however, a method of **operative treatment** has gradually developed that has given not only temporary relief, but in a surprisingly large percentage of patients has led to permanent cures. Unfortunately, a large number of the women with leukoplakic vulvitis refused any operative measures. In carcinoma of the vulva the number who refused treatment was smaller, but approximately 25 per cent. were in such bad physical condition or had such extensive involvement that nothing more than a simple vulvectomy could be done. If at present a radical operation can be done in 75 per cent. of vulval cancers, in spite of the fact that the disease was present for longer than a year and that many had palliative treatment elsewhere, it certainly speaks well for the possibilities of accomplishment by this method.

*Leukoplakic vulvitis* is permanently cured by **vulvectomy** in all but a few cases. Occasionally a secondary incision is required. In weighing in the balance the final results of vulvectomy in the treatment of leukoplakic vulvitis, it cannot be denied that some of these patients complain of a disagreeable feeling of tightness about the vulval skin and occasionally also of some irritation about the urethra from the scratching of the hairy skin to which it is approximated. Dyspareunia and pain on defecation, due to vaginal and rectal postoperative stricture—formerly one of the chief drawbacks to these operative procedures—are no longer to be dreaded since Taussig has been doing the posterior vaginal flap and double anal bridge operation. All in all, the operative results, both immediate and late, must be termed highly satisfactory. Since he has had but 1 operative death in 52 vulvectomies for leukoplakic vulvitis and that in a patient 70 years of age from embolism on the fourteenth day after operation, the author feels that there can certainly not be said to be any special danger from the surgical procedure.

In *carcinoma of the vulva*, the clinician is faced in his follow-up of cases with the fact that this is a disease not merely of old age, but of extreme old age. Approximately 60 per cent. of the women were over 60 years and 30 per cent. over 70 years of age. It is, therefore, not fair to consider every death that occurs in the 5- or 10-year period following operation as a failure to effect a permanent cure.

Out of 112 cases of vulval under consideration in this review, 76 were seen before 1929. During this period a variety of procedures were employed: radiation, simple vulvectomy, vulvectomy with the removal of superficial glands, and vulvectomy with double-sided Bassett operation. A comparison

of 5-year results reported in 1929 and borne out by subsequent reports showed definitely the great superiority of the radical gland removal over any other measures. In this first series it showed 81 per cent. 5-year cures with the Bassett operation compared to 30 per cent. where only the superficial glands were removed, and no cures with radiation or simple vulvectomy.

With an operability ratio of 75 per cent. and a primary mortality of only 4.6 per cent., the treatment of cancer of the vulva gives, with the possible exception of cancer of the uterine body, the most favorable prognosis of any form of malignancy in the genital tract.

Radiation, vulvectomy and superficial gland operations with vulvectomy have no place in the treatment of vulval cancer except as palliative measures. Three of 4 such cases can and should be subjected to the **double-sided Bassett gland excision with vulvectomy**, and approximately two-thirds of these will remain well for longer than 5 years.

F. H. Falls does not believe that **radium** should be used as a curative agent in carcinoma cases, but states that it is helpful to radiate with the radium plaque the skin of the inguinal canal before operation. His plan is to use small doses of radium by the radium plaque method, moving the plaque along the inguinal canal, about 200 mg. hours to each side, about 3 weeks before he plans to do the Bassett operation. He also follows up his operative procedures with x-ray therapy in all cases, paying particular attention to the radiation of the inguinal and iliac glands and the areas where metastases may occur.

**KRAUROSIS.**—During the past 8 years, P. J. Kearns (Canad. M. A. J. 33:48 (July) 1936) observed 17 cases of carcinoma of the vulva, 14 of which were sectioned and treated. Four of these showed a definite origin in leuko-

plakia. The chief clinical symptom in all cases of leukoplakia was pruritus, whereas in kraurosis the chief complaints were of dyspareunia, soreness and bleeding, and in carcinoma or a tumor of the vulva, with pain and bleeding. It is his belief that all cases of kraurosis vulvæ have a previous supertrophic or leukoplakic stage, and if this hypertrophy is prolonged, a progressive leukoplakia will develop, which will go through the stages of metaplasia and cancer formation. If, however, atrophy ensues, the leukoplakia progressively gives rise to kraurosis and the involved skin becomes thinner and thinner, resembling parchment. The surface becomes dry, scar-like and brittle. The shrinkage in this cicatricial sclerotic tissue produces a stretching of the skin over the nymphæ. The latter may entirely disappear, as may also the frenulum of the clitoris. The vestibule of the vagina becomes funnel-shaped and narrow, causing dyspareunia and pain on examination, because the diseased skin is easily torn and fissured.

*Histologically*, kraurosis shows an atrophy in all layers of the epidermis, especially of the horny and the lowest layers. In the outer and reticular layers of the cutis occurs, allowing the epidermis and cutis to lie in flat adjacent layers. In the outer and reticular layers of the corium, in contrast to the edema of leukoplakia, a homogeneous hyalinized material is seen, which spreads diffusely throughout the subcutaneous tissue, fat, elastic fibers, hair follicles, glands of the hair follicles, sebaceous glands, and sweat glands. These structures gradually disappear. If large sections are taken through the vulva, these atrophic changes can be seen and connected with remnants of leukoplakic areas. In the hypertrophic or leukoplakic stage, pruritus is a common symptom, but in the atrophic stage or kraurosis, soreness and bleeding are the troublesome features. The symptoms

of *pruritus* may be relieved by resection of the perineal nerves in the vulva.

**LICHEN PLANUS.**—E. Hunt (Brit. J. Dermat. 48: 53 (Feb.) 1936) discusses 73 cases of lichen planus of the vulva, of which 33 showed some degree of atrophy or contraction of the vulva, *viz.*, “kraurosis.” The *diagnosis* of a lichen planus eruption is often fraught with difficulty when lesions of a rarer type predominate. Lesions were confined to the vulva and adjacent parts in only 15 cases of the present series, and in all the others lichen planus lesions of various types were present at sites remote from the vulva. When it is recalled that a lichen planus eruption may cause no direct or very slight subjective symptoms, the possibility arises that many patients suffering from lichen planus of the vulva never seek advice and that in other cases advanced atrophic changes of the vulva may be found in which symptoms have developed only at a later stage owing to the atrophic changes that have occurred.

No causative factors for leukoplakia vulvæ have been determined. The *etiology* of lichen planus is obscure, but ovarian dysfunction has never been sug-

gested as a predisposing factor, since the eruption occurs in both sexes. Derangements of the nervous system following debilitating illness, anxiety, worry and overwork have long been recognized as associated factors in the causation of lichen planus, though many cases are on record in which none of these factors could be determined.

Leukoplakia vulvæ is stated to be a precancerous condition. Lichen planus is not a precancerous condition. Certain factors may be considered to contribute to the development of epithelioma in atrophic lichen planus lesions on the vulva. When atrophy of the vulva occurs, there is increased friction of atrophic surfaces due (1) to the suppression of the secretions, owing to atrophy of the glands, with which the skin of the vulva is well supplied and which keeps the parts well lubricated, and (2) to the absence of the labia minora, which normally provide a soft buffer between the larger labia and protect the vestibule. In addition, the dryness of the atrophic surfaces is in many cases aggravated by prolonged and/or ill-advised applications for the relief of itching.

## OBSTETRICS

**PREGNANCY.—DATE OF CONFINEMENT.**—It is customary to add 280 days to the first day of the last period in calculating the day of delivery. However, F. A. Wahl (München. med. Wchnschr. 83: 311 (Feb. 21) 1936) observed that the date thus computed only rarely coincides with the actual date of delivery and also that the period of 280 days is too short in many cases. He also gained the impression that the date of birth is to a certain extent dependent on the menstrual cycle. He made studies in 5000 obstetric cases,

investigating (1) how often a mature child is born 280 days after the first day of the last menstruation, and (2) whether there is a relationship between the computed date of birth and the menstrual cycles.

A mature child is born after 280 days in 65 per cent. of women with a cycle of 28 days. However, in women in whom the menstrual cycle is longer than 28 days, the delivery takes place at a later date in more than 75 per cent., whereas in women with a menstrual cycle of less than 28 days, the calculated

date is not reached in approximately 80 per cent. The author concludes from these observations that in women with a menstrual cycle of 28 days or longer, measures to induce delivery can be postponed for a while in case the gestation has gone beyond the calculated term; whereas in women with a short menstrual cycle, it is advisable to take measures sooner. Moreover, in forensic problems in which the average length of pregnancy has to be estimated, the dependence of the length of the period of gestation on the length of the menstrual cycles should be given consideration.

**CONTRACEPTION.**—In a period of approximately 6 years, from March, 1928, until January, 1934, 4000 patients were admitted to the Maternal Health Clinic of Cleveland for advice as to family regulation. A study of the results obtained in this clinic was undertaken by R. A. Robishaw (*Am. J. Obst. and Gynec.* 31:426 (Mar.) 1936).

The routine of the clinic is to subject the woman to careful pelvic examination, determine the most suitable contraceptive technic, and teach the manipulation of any mechanical advice prescribed at the first visit. Various methods of contraceptive treatment are prescribed according to the indications. Preference is given to the **diaphragm pessary** used in conjunction with **lactic acid jelly**. Eighty-eight per cent. of the group received such treatment.

Several types of occlusive pessaries have been prescribed for these patients. By far the most commonly employed type has been the round spring diaphragm pessary. The size of these pessaries, as expressed in the diameter of the device measured in millimeters, has varied greatly, from size 60 to size 95, but sizes 80 and 85 have been more frequently used. Many patients have been fitted with diaphragm pessaries with the flat spring rim of the Mensinga

type. Among the pessaries of the cervical cap type, the Mizpah has usually been employed. A very few patients have been equipped with Dumas pessaries. Most cases in which a Matrisalus pessary with its characteristic supporting rim might have been indicated have seemed better treated with a Mizpah pessary or mechanical protection for the husband. In every instance, the pessary is prescribed to be applied with lactic acid jelly in apposition to the cervix and plentifully applied to the rim in its entire circumference. With scarcely an exception, the pessary has been fitted with its concave surface uppermost. Great effort has always been expended to teach identification of the cervix through the occluding pessary. This has almost always been possible. A very few patients have been unable to perform this check of the cervix, usually because of an obese abdominal wall or short intravaginal portion of the cervix. The very inaccessibility of the cervix has made it less likely to elude the inserted diaphragm pessary, which is the only type prescribed for such patients. A minimal postcoital interval of 6 hours is always advised before the pessary is removed and not then until after a **douche** of at least a quart of plain warm water has been taken. Pregnancies have apparently occurred when the technic has been varied by removal of the device immediately or very shortly after intercourse or by removal of the pessary even after a considerable period of time has elapsed without douching. Preference is given the fountain syringe as the instrument for douching, although careful douching with the bulb syringe has been permitted. Emphasis is always given to the superiority of the reclining position on douching.

The wife has always been equipped with some **spermicidal preparation** when **condoms** have been prescribed



for the husband. Preference has been somewhat in favor of suppositories over jellies as being easier to manipulate. The patient is directed to insert the spermicidal agent 10 minutes before coitus to allow ample dispersion of the medicament. The suppositories are of cocoa butter base, containing as the most active ingredients **quinine** and **salicylic acid**. Care is exercised always to dispense a fresh, carefully compounded preparation, capable of prompt dispersion. Whenever **jelly** has been prescribed in this series as an adjunct to the condom, a formula with 1 per cent. **lactic acid** and 5 per cent. **boric acid** in a glycerite of starch base has been given. In almost every instance, the sheaths are of rubber and are intended to be used a single time only. Instruction is given as to the technic of testing, applying and removing the condom. An immediate **vinegar douche** is advised in the event the condom is broken in the vagina.

In the few cases in which the spermicidal activity of a jelly or suppository has constituted the only treatment prescribed, a douche has usually not been advised until several hours after coitus. Lately, with increasing frequency, an immediate **vinegar** or **acetic acid douche** has been prescribed. The suppository has almost always been of the type described above. The jelly has almost always been the lactic acid jelly previously mentioned, although in a few cases, a **jelly** containing **chinosol** has been used.

Forty-one instances of pregnancy are recorded as failure of the method prescribed. In this group are considered all inexplicable pregnancies. Some of these failures might be avoided in the future with increased skill in the matter of determining the most suitable contraceptive treatment for various indications.

The value and necessity of routine check-up after the patient has been using the method 3 months is made a matter of concern to patient, doctor, nurse, and referring agent wherever possible. The follow-up of the nursing staff is intensive to the end that this return shall be affected. At the 3 months' routine reexamination, many difficulties may come to light. Such are usually easily removed at this time, before the patient sustains failures, prejudice, or indifference. Sometimes the method needs to be supplanted, sometimes the size of the pessary needs to be altered, particularly if the fitting has been done premaritally or early in the postpartum career, and sometimes the technic needs to be corrected. Patients are seen routinely at yearly intervals by the physician for examination after the first check-up.

Forty-one in a group of 4000 cases have sustained inexplicable pregnancies and are considered failures of the method prescribed. Fifty-nine have conceived through misapplication of the method.

**COMPLICATIONS.—Abortion.—***Legality in Soviet Union.*—The safety of legalized abortions as practised in the Soviet Union has recently been questioned. On June 27, 1936, the Central Executive Committee and the Central Peoples' Health Committee of the Soviet Union passed a new law prohibiting abortion except in the presence of stringent indications; thus, it completely reversed its stand of 1920, when it legalized artificial abortion.

The medical profession in the Soviet Union had an unusual opportunity to observe the harmful effects, both early and late, of artificial abortion. G. A. Bakscht, the head of the First Gynecologic-Obstetric Clinic of the Leningrad Medical Institute (Sovet. vrach. zhur. (June) 1936) states: "The accumulated

experience since 1920 furnishes abundant proof that artificial abortion is a serious evil and that the operation, even when performed *lege artis*, leads to a number of injurious effects." Trauma and infection have always constituted a real danger in operative interference with the normal process of labor. The same holds true with even greater force in the case of artificial abortion. The organism of the woman in the first months of pregnancy has not acquired those protective properties which guarantee it a physiologic puerperium. In discussing the operative trauma, Bakscht states that the incidence of perforation of the uterus amounted to from 0.01 to 0.11 per cent. This accident not infrequently calls for an immediate laparotomy, in order to ascertain probable injury to the intestine, the urinary bladder or the mesentery. Occasionally the uterus has to be sacrificed in a young woman. According to Ulyanovsky (cited by Bakscht), tears of the internal os occurred in 10.5 per cent. and led to cicatricial contractures and even to a complete atresia, or served as a portal of infection of the parametrium. Too energetic curettage of the uterine mucosa traumatizes the basal membrane, with the consequent atrophy and depression of the menstrual function.

While microorganisms enter the uterine cavity after the fourth day in the normal puerperium, about the time of the formation of the protective granulation zone, bacteria were found to be present in the uterine cavity after an artificial abortion on the second day after the operation and their number rapidly increased on the third and fourth days. This is manifested clinically by the frequency of "mild" fever. The high incidence of postabortive fever (40 and 50 per cent., according to Rusin) depends on the considerable number of repeated abortions, with the attendant subinvolution and latent infection. Chronic

pelvic infection was present in 12.8 per cent. in a follow-up study of 1500 cases of artificial abortion.

The extent of biologic trauma is rather difficult to estimate. The introduction of two new glands of internal secretion, the corpus luteum and the placenta, undoubtedly call for especial adaptation on the part of the rest of the endocrine-vegetative system. The effect of the sudden interruption of pregnancy must be to upset the new equilibrium and lead to endocrine-vegetative upsets and disturbance of the menstrual function and the libido. This is of particular significance when interrupting the first pregnancy in women with an asthenic-hypoplastic constitution. It tends to stabilize infantilism and result in sterility even in the absence of a pelvic infection. Artificial abortion is an important etiologic factor in extra-uterine pregnancy.

*Treatment.*—T. N. Parish (J. Obst. and Gynaec. Brit. Emp. 42: 1107 (Dec.) 1935) presents an interesting review of 1000 cases of abortion in England with a mortality rate of 1.8 per cent. He found that 203 of the women had no living children and 173 were pregnant for the first time; 207 of these women had 1 living child and only 136 had 6 or more children. Admittedly, 485 of the women had induced abortion by one means or another, varying from the employment of an abortionist to the use of slippery elm bark. Most of the deaths that occurred in the entire series were in this group. In another group, of 246 cases, abortion was the result of various diseases or conditions, the most common, in order, being uterine displacement, accidents, pulmonary diseases, pelvic diseases, lacerated cervix and renal diseases. There was no intervention in this group, and there were no deaths. Of the 1000 cases under review, infection was present

in 48.3 per cent. on admission to the hospital.

For the group of 151 cases of *threatened* abortion, the plan of treatment was to place the patients completely at rest, giving 0.016 Gm. ( $\frac{1}{4}$  grain) of **morphine** if pains were present, and to defer pelvic examination if the diagnosis was clear. With this treatment 57 per cent. of the patients with threatened abortion were discharged still pregnant. For the 148 cases of *inevitable* abortion, no treatment other than **ergot** was given unless there was a special indication. If the abortion was not progressing, an **enema** was given followed by 3 injections of 0.5 c.c. (8 minims) of solution of **posterior pituitary** every 2 hours. When this treatment failed to complete the abortion, the **uterus** was **evacuated**. In 72.9 per cent. of the cases of inevitable abortion, completion occurred spontaneously or with the assistance of drugs. Of 481 cases of *incomplete abortion*, infection was present on admission in 52 per cent. **Expectant treatment** was followed until the fever subsided, unless hemorrhage necessitated more active measures. Five days was found to be a satisfactory period to allow between the subsidence of fever and **evacuation** of the uterus. When the temperature, however, failed to return to normal in a week, the **retained products** were removed from the uterus with as little trauma as possible. If it was necessary to dilate, great care was taken not to split the cervix, to avoid any pathway for the entry of microorganisms into the parametrium. If the uterus could not then be evacuated digitally, a blunt **curet** was used only to explore the uterus. When drawn gently over the uterine surface, if an obstruction was located, a slightly firmer pressure was made to remove it, but curettage was not performed. The uterus was flushed with a **mild antiseptic**

**solution**; when retained products ceased to come away with the flushings, the curet was abandoned.

**Operative intervention** was required in 461 cases to evacuate the uterus completely: 7.2 per cent. of these later showed some rise in temperature, while in only 1.7 per cent. of the spontaneously completed abortions was there any exacerbation of infection. Active infection was present in more than half of the cases of *complete abortion* on admission to the hospital; if the temperature did not fall with **bed rest** in such cases, treatment by means of **intrauterine injections of glycerin** was undertaken. All but 1 of the 18 patients who died were infected at the time of admission; in one of the fatal cases, septicemia became apparent 6 days after curettage for subinvolution.

**INFECTED ABORTION.**—*Treatment.*—A study of 445 cases of abortion observed at Cleveland City Hospital during a period of  $2\frac{1}{2}$  years is presented by J. L. Reycraft and S. F. Moore, Jr., (Surg. Gynec. and Obst. 62:989 (June) 1936). Over this interval the method of treatment was fairly uniform and affords suitable opportunity for appraisal of results.

The general tendency in treatment is toward a policy of nonintervention. It is recognized that invasion of the uterus, especially with active or potential infection, may be exceedingly hazardous. However, it is believed that circumstances justify this risk in some instances.

The importance of **blood transfusion** as a life-saving measure in extreme exsanguination and as a therapeutic procedure in the presence of infection is properly stressed.

*Intrauterine manipulation is avoided* in all cases if practical. Opportunity is allowed for spontaneous completion, unless hemorrhage is severe or other conditions warrant immediate intervention.

However, if the abortion is still incomplete after the patient has been afebrile for 48 hours, it is thought that there is no advantage in delaying completion for a longer time.

Of the 445 cases observed, 272 were treated by some type of **operative evacuation** of the uterus. It is shown that the optimal time to empty the uterus, when infection has been present is after the temperature has been below 100.4° F. (38° C.) for 48 hours. It is important to carry out this procedure with a minimum of trauma, avoiding dilatation of the cervix and curettement if possible. When the uterus is emptied at the proper time in properly selected cases and with minimal trauma, the morbidity following operative procedures is not excessive and is of a benign nature.

This series presents a total of 21 deaths—a gross mortality of 4.72 per cent. One-third of these deaths occurred within 24 hours of the patients' admission to the hospital. Only 3 followed operative treatment at City Hospital.

It would appear from this study that the mortality and morbidity in accidental or criminal abortion could be reduced materially by more intelligent management of each case from its onset. Such management would include the following of certain principles which experience has shown may not be violated without ill results.

**THERAPEUTIC ABORTION.—X-rays.**—Ten years ago the Gynecological Service and the Radiotherapy Department of Mt. Sinai Hospital attempted a preliminary series of therapeutic abortions by means of *x-ray*. The results obtained were sufficiently satisfactory to warrant a continuation of the method. M. D. Mayer, W. Harris and S. Wimpfheimer (Am. J. Obst. and Gynec. 32:945 (Dec.) 1936) report the results of 10

years' experience with the records of 200 fully studied consecutive cases.

The authors believe that the abortion is caused by the death of the fetus as a direct result of the radiation, rather than through any effect on the ovaries or the placenta. Since young growing cells have a greater sensitivity to x-ray than older cells, the fetus can be destroyed without any considerable damage to the uterine musculature and the parametrial tissues.

The *technic* used throughout this series of cases was uniform. Sixty per cent. of a skin erythema dose (600 r. measured in air is considered an erythema dose) was given to the center of the uterus. Calculation of the amount that had to be given to the skin to obtain this dose was determined by making outlines of the pelvis and estimating the quantity necessary to obtain the desired dose in the uterus, according to the methods of Holfelder and Weatherwax. In the average case with an anteroposterior pelvic diameter of 20 cm., 2 opposing fields each receiving 600 r. in air will suffice if the apparatus will deliver 35 per cent. S.E.D. at 10 cm. depth. When the anteroposterior diameter is larger than 20 cm., compression cones or strapping of a pendulous abdomen will aid in reducing the distance to the uterus. When adequate reduction of the distance is not possible, additional portals of entry (3 to 6) may be required.

The apparatus should be calibrated by a competent physicist and, if possible, a constant reading dosimeter between the tube and the patient will aid in giving the correct dosage. The physical factors are 180-200 K.V., 50 cm. F.S.D., filter 0.5 mm. copper, 1 mm. aluminum; size of portals average 15 x 20 cm. (suprapubic and sacral, including the adnexa). The treatment should be given on 2 or 3 successive days.

A **mild cathartic** is given on the evening before treatment and the bladder is always emptied immediately before treatment is administered. The outline of the uterus is mapped out on the anterior abdominal wall with a colored pencil and the central beam is directed through the middle of the fundus.

When there is a discrepancy between the length of amenorrhea and the size of the uterus, the authors advise a radiograph of the pelvis to determine if possible the size of the fetus.

The presence of fibroids is not a contraindication to treatment.

If continued growth, etc., show that the fetus is still alive after 4 weeks, radiation may be repeated, provided that the size of the uterus at that time is not larger than that of a 4 months' pregnancy. There are several instances in this series in which this procedure was carried out successfully.

The pregnancy must never be permitted to continue to term following x-ray treatment, because of the definite possibility of the birth of an abnormal child.

The authors report 200 ward patients with a clinical success in 96 per cent. and an ideal success in 90 per cent.

The method is recommended for pregnancies of not more than 14 weeks' duration, in women who are suffering from a serious lesion which would make surgical interruption very dangerous and who should not again become pregnant. This is particularly valid for women over 35 years of age.

The method has no mortality and remarkably low morbidity, but it does require the closest coöperation between clinician, radiotherapist, and gynecologist, as well as scrupulous observation, control, and follow-up of the patient.

If the treatment should fail, under no circumstances should the pregnancy be permitted to continue.

The clinical picture is that of a missed abortion with a latent interval averaging about  $4\frac{1}{2}$  weeks.

**THREATENED ABORTION.—Treatment.**—The hormonal theory of the onset of labor is important in the treatment of threatened abortion. F. H. Falls, J. E. Lackner and L. Krohn (J. A. M. A. 106:271 (Jan. 25) 1936) discuss the value of **progestin** in the treatment of *threatened abortion*. As gestation advances, the amount of estrogenic substance increases, reaching a maximum at term. In this way the balance between the estrus-inducing principle and

progestin is disturbed; the estrogenic principle becomes dominant and sensitizes the uterus to the oxytocic principle of the posterior lobe of the pituitary gland and labor ensues. The authors believe that the irritability of the sympathetic nervous system, the intrinsic nervous mechanism of the uterine wall, and possibly the hormones from the thyroid or the adrenal glands are factors which play a part in the onset of labor.

Patients with threatened abortion received 1 rabbit unit twice daily until all symptoms subsided or the patient aborted. In the treatment of *habitual abortion* 1 rabbit unit of **progestin** was given **prophylactically** twice weekly from the time the diagnosis of pregnancy was made until the thirty-second week of gestation. Of the 41 cases of threatened or habitual abortion, 34 were treated successfully with this drug. In order to demonstrate the inhibiting action of progestin in the human being experimentally, the authors introduced a hydrostatic bag into the uterus of a seventh day parturient patient under sterile precautions. Kymographic tracings of the uterine activity were obtained in this way. Normal uterine contractions and the effects of solution of pituitary, estrogenic substance and progestin on the human puerperal uterus were investigated. The experiments were allowed to proceed for periods of 2 and 3 hours, during which time continuous tracings were made.

The estrogenic substance **progynon B** stimulates contractions of the puerperal human uterus in doses of 20,000 and 40,000 rat units.

One rabbit unit (Corne) of **progestin** inhibits human uterine contractions in a seventh day parturient patient.

One rabbit unit (Corner) of the lutein hormone **progestin** completely nullifies the effect of 1 c.c. of solution of pituitary, whether given before or

after the response to the injection of solution of pituitary.

The hypodermic injection of  $\frac{1}{4}$  grain (0.016 Gm.) of morphine sulphate not only failed to diminish contractions of the human puerperal uterus produced by the injection of 1 c.c. of solution of pituitary, but actually seemed to augment them. [According to this, morphine is contraindicated in the treatment of threatened abortion.—EDITOR.]

**Anemia.**—Studies were made by F. H. Bethell (J. A. M. A. 107: 564 (Aug. 22) 1936) of the blood of 66 healthy young women during the last trimester of pregnancy, and similar observations were obtained from 50 healthy nonpregnant women of the same age group. In 70 per cent. of the pregnant subjects the blood values were too low to be accounted for solely by increased plasma volume with consequent blood dilution.

Anemia in pregnancy is commonly due either to preëxisting iron depletion or to an inadequate intake of protein of high biologic value during gestation. Rarely, it is of the *pernicious* type amenable to **liver** or **stomach therapy**.

A lack of iron may be recognized before the development of actual anemia by the presence of a lowered color index or of red blood cells of less than normal size. In such cases the administration of an **inorganic iron** preparation in adequate dosage is indicated.

*Anemia dependent on protein deficiency* characterized by a normal color index and by red blood cells of normal or increased volume, may be prevented or corrected by a suitable **diet**.

**Types.**—Various types of anemia occur during pregnancy. The first and most common is the so-called "*physiologic anemia*" of pregnancy. A second type of anemia in pregnancy occurs in women who have a subnormal hemoglobin in early pregnancy and when the "*physiologic anemia*" occurs, the drop

in hemoglobin is so great that symptoms and signs of anemia occur, which may clear up after delivery or may persist. This is usually a *microcytic type* of anemia with the corpuscular volume ranging between 70 to 80 c.μ. This group forms the vast portion of anemia in pregnancy, and the patients, as a rule, have no symptoms or signs of the condition.

A third type is rare and is characterized by a larger cell, ranging from 90 to 130 c.μ. These patients usually have symptoms and signs of anemia and at times seem to have a toxemia of pregnancy, as indicated by edema and albuminuria. The blood smears show all the characteristics of a pernicious anemia and occasionally the differential diagnosis is difficult. As a rule, there are no neurologic findings and the characteristic increase in reticulocytes does not occur after administration of liver. Such patients were formerly designated as having *pernicious anemia of pregnancy*. The mortality rate was quite high.

The means for the hemoglobin concentration in pregnancy, according to F. L. Adair, W. J. Dieckmann and K. Grant (Am. J. Obst. and Gynec. 32: 560 (Oct.) 1936), are 11.56 grams per 100 c.c. of blood; for the cell volume, 37.31 volume per cent.; and for the erythrocyte count, 3.77 million.

The minimum standards for normal pregnancy are 10 grams of hemoglobin per 100 c.c. of blood; 33 volumes per cent. for the cell volume; and 3.36 million for the erythrocytes.

Eleven and six-tenths per cent. of their pregnant patients have an anemia, according to their standards, but if the standards for the nonpregnant patients are used, 63.2 per cent. must be classed as anemic.

A normal decrease and increase in the hemoglobin, cell volume and erythrocyte count occurs during pregnancy.

These changes cannot be altered by treatment. The fluctuation may amount to 2, 3 or even 6.0 grams of hemoglobin within a period of 4 to 6 weeks.

Knowledge of these marked fluctuations should suggest great caution in attributing an increase in the hemoglobin concentration, cell volume and erythrocyte count to any previous therapy.

An adequate amount of transfused blood will raise the hemoglobin concentration to normal permanently and relieve all the symptoms and signs of the anemia.

**Blood transfusion** during pregnancy, if done properly, has no deleterious effect on the mother or the fetus. It has not caused premature labor.

The prevention of anemia of pregnancy is easier than the cure. An **adequate diet**, with **proper hygiene**, is the best *prophylaxis*.

A normal hemoglobin content is essential for the normal function of the organs of the body. Toxemia is less likely to occur; the patient is better able to tolerate blood loss and the strain of labor; her tissues have more resistance; she is less likely to become infected; and her recovery after delivery is more rapid.

**Diabetes.** — *Treatment.* — A diabetic woman who becomes pregnant is an abnormal woman, who requires special care and consideration. In all probability the baby is going to be large, for 60 per cent. of such babies weigh more than 8 pounds (3.6 Kg.), as compared to 9 per cent. of babies of normal mothers. This means a more difficult labor if the mother is allowed to go to term. The fact that the baby is large does not mean that it will be healthy; on the contrary, it may be "flabby" and born dead. The incidence of stillbirth in cases in which the mother is diabetic is many times that occurring in normal deliveries. Not

only is the child likely to be injured by the difficulties of labor, but it often succumbs *in utero* to the abnormal state existing in the last few weeks of pregnancy. For this reason, L. M. Randall and E. H. Rynearson (J. A. M. A. 107: 919 (Sept. 19) 1936) advocate delivery by **Cesarean section** in the thirty-sixth or thirty-seventh week of pregnancy, at which time **sterilization** can be accomplished if permitted and advisable.

During the third trimester of pregnancy the pancreas of the infant has been attempting to supply the insulin the mother lacked. After birth, the child's pancreas continues to overfunction and produces hypoglycemia.

The infants, therefore, should be fed immediately after birth by administering a solution of **dextrose by rectum**.

The authors report the successful delivery in 7 successive cases of diabetic mothers. In view of their experience, they have instituted the following general plan for the management of the infant of the diabetic mother for the first few days of its life. The length of time that this program will need to be maintained will vary and depend on the degree of prematurity, the length of time before food and fluid can be taken by mouth, and the duration of the period of readjustment of pancreatic function.

The concentration of sugar in the blood of the mother, the infant, and the umbilical cord should be estimated immediately. Five c.c. of 10 per cent. solution of **dextrose** is given by mouth if possible; otherwise it is administered intramuscularly.

**Hydatidiform Mole.** — *Diagnosis.* — F. J. Schoeneck (Am. J. Obst. and Gynec. 32:104 (July) 1936) tried to determine the minimal amounts of urine, at various stages of pregnancy, required to produce positive Friedman reactions. With such normal standards established,

a *quantitative Friedman test* is made available. Nonpregnant dogs weighing at least 1500 Gm. and between 16 and 18 weeks of age were used. All animals were of the same or similar breeds and were obtained from the same source. Fractional intravenous injections of known pregnancy urines were made in dilutions of 0.025, 0.05, 0.1, 0.5, 1 and 3 c.c., and so on. From 2 to 6 rabbits were used for each test. The animals were laparotomized 48 hours after the injections. Corpora hemorrhagica or fresh corpora lutea were the criteria for a positive reaction. In general, the smallest amounts gave positive reactions between the sixth and tenth weeks of pregnancy. Sixty-seven quantitative determinations were made on 41 known pregnant patients. The smallest amount of urine that gave a positive reaction in normal pregnancy was 0.05 c.c. The maximal amounts varied between 3 and 5 c.c.

The results of the quantitative test in 4 cases of hydatidiform mole and 1 of chorioepithelioma are given. A wide variation (between 0.0063 and 5 c.c.) is noted in the mole cases. Two cases of hydatidiform mole showing marked hyperexcretion of the substance responsible for the reaction exhibited typical textbook specimens of hydatidiform mole, *i. e.*, grape-like masses of vesicles, whereas in the other two instances the specimens were made up principally of fibrous tissue with comparatively few vesicles. The composite results of 84 quantitative tests on 56 pregnant patients show that the group in which nausea and vomiting were absent required more urine to produce positive results than did the groups in which these symptoms were present.

The contrast is especially marked between the nausea and vomiting group and that including the pernicious vomiting cases. In the pernicious vomiting

cases, as the symptoms abated, the amount of urine required to produce a positive reaction increased. While there is insufficient evidence to advance a hormone explanation of the cause of vomiting of pregnancy, the evidence seems important enough to warrant continued investigation.

**Hypercholesteremia.** — R. A. Bartholomew and R. R. Kracke (Am. J. Obst. and Gynec. 31:549 (Apr.) 1936) believe that the hypercholesteremia of pregnancy is probably a normal physiologic response to meet the requirements of rapid cell growth in the fetus and prepare for lactation. An excessive degree of hypercholesteremia of pregnancy is probably due to hyperpituitary or hypothyroid activity and is further increased by a diet high in cholesterol-containing foods. Hypercholesteremia is probably the fundamental basis for the *toxemias of pregnancy*. It probably is responsible for *nausea and vomiting of pregnancy*, through an increased secretion into the bile until storage of this material can take place in the reticulo-endothelial system.

Excessive storage in the liver in the first half of pregnancy is probably the cause of excessive fatty change in the periphery of the liver lobules, with subsequent central necrosis in the inner zone of the lobules, which is so consistently found in fatal cases of pernicious vomiting of pregnancy. Excessive storage in the placental arteries, with resulting vascular changes, is the predisposing cause of *infarction in the placenta*. Thrombosis or rupture of a placental artery, occurring either spontaneously or produced by the trauma of fetal movements, is the exciting cause of acute infarction in the placenta. Acute or subacute infarction in the placenta results in autolysis of the affected tissue, with the liberation of peptone, guanidine and histamine as toxic split products of



placental protein. The amount and location of the infarction, the degree of vessel obstruction and the rapidity of autolysis determine whether *preëclampsia* of mild or severe degree, *eclampsia* or *premature detachment of the placenta* will occur.

If hypercholesteremia is the fundamental basis for the *toxemias of pregnancy*, it would seem that *prophylaxis* should be directed toward neutralizing the effect of excessive secretion of cholesterol into the intestinal tract through the bile and preventing excessive storage of cholesterol in the endothelial system by the administration of **thyroid extract** or **iodine** and **restricting** the use of **fats** and **cholesterol-containing foods** during pregnancy.

**Perforations of Uterus.**—L. Gerhardt (Ginek. polska 14:627, 1935) analyzes 16 cases of uterine perforation. In 12 cases the perforation was caused by a physician and in 3 by a midwife. In one case its cause could not be determined. Of the 12 perforations caused by physicians, only 2 were caused by gynecologists. It may therefore be concluded that the majority of such perforations are caused by physicians without special and technical training.

The author reports the cases in detail. Nine of the women were between 20 and 30 years of age, 5 between 30 and 40, and 2 under 20. Six were primiparas and 10 were multiparas. Seven were operated upon within 6 hours after the perforation and the others after from 8 to 24 hours. In 2 cases there was a 6 weeks' pregnancy; in 6 cases, an 8 weeks' pregnancy; in 5 cases, a 12 weeks' pregnancy; in 2 cases, a 16 weeks' pregnancy; in 2 cases, a 16 weeks' pregnancy; and in 1 case, a 20 weeks' pregnancy.

In 11 cases the uterus was injured in an attempt to interrupt pregnancy; in 4 cases, in the removal of tissue remain-

ing after abortion; and in 1 case, in the evacuation of a vascular mole. In 4 cases the perforation was caused by a Hegar dilator; in 3, by a Winter forceps; and in 2, by a curette. In 9 cases the perforation was in the cervix; in 6, in the anterior wall of the uterus; and in 1, in the posterior wall. Injury of the omentum occurred in only 2 cases; and the intestine escaped through the perforation in only 1 case.

**Treatment.**—In 4 cases the **perforation** was **sutured** after the removal of abortion material through the opening. **Supravaginal hysterectomy** was done in 7 cases and **total hysterectomy** in 1 case. In 2 cases **exploratory laparotomy** was performed in the tissue left after abortion was removed through the vagina. Two cases were **treated conservatively**.

Of the fourteen patients treated surgically, only 1 died. The total mortality was therefore 7.1 per cent. However, as the one death occurred from tuberculosis 6 days after the operation, there was no operative mortality.

The good results are attributed by the author to the absence of infection and the fact that every case was treated individually with the following factors in mind: the qualifications of the person who caused the perforation (physician, midwife, untrained person), the site and character of the perforation, the length of time that had elapsed since the injury, the age and condition of the patient, and the conditions at the time of the perforation (possibility of infection).

On the basis of this material the author concludes that only injuries of the cervix without parametrial or peritoneal injury can be treated conservatively. In all other cases of perforation laparotomy should be performed with preservation of the uterus when possible.

**Pyelitis.**—*Etiology and Pathogenesis.*—In a further report, D. Baird (J. Obst. and Gynaec. Brit. Emp. 42:735 (Oct.) 1935) points out that dilatation of the upper urinary tract occurs in nearly every pregnant woman. It is usually more marked on the right side than on the left and affects the calyces, renal pelvis, and ureter down to the level of the pelvic brim, where the ureter narrows suddenly. In its pelvic portion the right ureter is undilated. On the left side, the calyces and renal pelvis are less frequently involved. The dilatation affects the ureter usually throughout its whole course, as a rule tapering gradually to the bladder, but in some cases narrowing abruptly at the pelvic brim.

On both sides kinks are usually seen, but on the right side they are much more pronounced than on the left and may be very acute. They are usually situated at the junction of the renal pelvis and ureter and cause definite narrowing of the lumen.

Lateral displacement of both ureters to the outer border of the psoas muscle is frequent in the second half of pregnancy. When this occurs, the ureter escapes compression until it crosses the psoas muscle at the level of the pelvic brim to gain access to the pelvis. When no lateral displacement occurs, the ureter lying along the psoas muscle is compressed for the greater part of its course, above the brim of the pelvis. If the abdomen is pendulous—in primigravidæ because of a contracted pelvis or spinal deformity and in multiparæ because of a lax abdominal wall—the point of compression is usually low, at the pelvic brim, but when the abdominal muscles are firm and the ureter is not displaced laterally, the ureter is flattened in its abdominal portion to a much higher level. Dilatation of the upper urinary tract is more marked in primigravidæ

than in multiparæ. Dilatation is found as early as the tenth week and at this stage is uniform throughout both ureters, involving the pelvic as well as the abdominal portions. It may be more marked on the right side even at this early stage. At the end of the fourth month, it is increased by the pressure of the pregnant uterus, especially on the right side. Up to the sixth month it increases. From then until term it decreases on the left side. On the right side the calyces, renal pelvis, and ureter down to the pelvic brim may dilate further or may become smaller. More commonly, the calyces and renal pelvis increase in size and the size of the ureter diminishes.

In conjunction with dilatation, stasis is usually found, although dilatation can exist without stasis and stasis may be present with very little dilatation. Stasis begins early in pregnancy, reaches its maximum as a rule at the sixth month, and diminishes near term. At the sixth month, although there is a marked disturbance of ureteral function, renal function may be better than later when the function of the ureter has improved since, because of the increased pressure of the uterus and the improved tone of the ureter, the intraureteral pressure rises and affects the function of the kidney adversely.

As the effect on the left kidney is almost negligible, symptoms of renal deficiency seldom develop during pregnancy. In 15 per cent. of cases pain referable to the urinary tract occurs because of disturbance of ureteral peristalsis.

Histological examination of the wall of the ureter above the point of compression has shown that no hypertrophy occurs in response to the obstruction but, on account of the atony, the ureter simply stretches. Because of the increasing pressure of the uterus, dilata-

tion and stasis would be progressive until the end of pregnancy if some other factor did not come into play. The tone of the ureter improves near term, but diminishes rapidly in the puerperium, especially in cases in which the dilatation and stretching reach a high degree. When the dilatation is only slight during pregnancy, the falling off in tone in the puerperium is much less. This suggests very strongly that the improvement in the cases with marked dilatation is due to a stimulus which is suddenly withdrawn after labor. The ureters subsequently regain their tone slowly, in proportion to the rate of disappearance of the dilatation. In some cases in which dilatation has been very great, the right urinary tract never returns to normal and the tone remains less than that of the left urinary tract which has been relatively unaffected.

It is now established that estrin sensitizes the uterine muscle to the action of pituitrin and that the estrin content of the blood rises as pregnancy advances, reaches its maximum just before term, and rapidly diminishes in the puerperium. It is possible that the variations in the estrin content of the blood during pregnancy and the puerperium influence the tone of the urinary tract in the same way as they affect the tone of the uterus.

It is claimed that in cases of albuminuric toxemia there is an excess of posterior pituitary hormone in the circulation (Anselmino, Hoffmann, and Kennedy). The fact that in this condition there is very little atony of the ureters suggests that the posterior pituitary hormone also plays a part.

D. Baird (*Ibid.* 42: 577 (Aug.) 1935) discusses pyelitis of pregnancy and its relation to changes in the upper urinary tract.

The investigation of the urinary tract in gynecological conditions was first un-

dertaken to compare the effect on the urinary tract of the presence of the gravid uterus in pregnant women with that of gynecological tumors of similar size in nonpregnant women. It is common knowledge that gynecological tumors, both inflammatory and neoplastic, are frequently associated with urinary symptoms, usually disturbances of micturition due to displacement of or pressure on the bladder, but it is not generally recognized that dilatation of the upper urinary tract may also occur in those cases. However, it is well-known that in cases of advanced carcinoma of the cervix, the ureters may be compressed in the parametrium or at the pelvic brim by the carcinomatous tissue, and complete suppression of urine, due to blockage of both ureters, is one of the recognized causes of death.

**Pelvic Cellulitis.**—Of 11 cases of pelvic cellulitis in which a urological examination was made, excretion was not delayed in 3 of salpingo-oöphoritis with very slight cellulitis. In 8 cases, cellulitis was extensive and there was a delay of excretion which was more marked on the left side in 5 and more marked on the right side in 3 cases.

**Ovarian Cyst.**—Only 1 of the 11 cases of ovarian cyst had no delay in excretion. This was the case of a para-II with a moderately-sized, soft cyst which floated about freely in the abdomen. When the cyst is adherent to the tissues in the neighborhood of the pelvic brim, dilatation and stasis are always found. The most marked example of this was a malignant ovarian cyst of moderate size adherent to the pelvic brim at the left side.

Simple cysts which are not adherent may cause dilatation and stasis in the upper urinary tract. It is possible that a disorder of the endocrine balance lowered the tone of the ureteral musculature, so that it was more susceptible to

pressure. This is probably what occurs during pregnancy.

In the cases in which the cyst fills the pelvis and reaches to the level of the umbilicus (*i. e.*, approximately the size of a 5 months' pregnancy), the ureter on the side most affected by the cyst can be demonstrated clearly by intravenous pyelography down to the pelvic brim, showing that the point of compression is at the pelvic brim. When the cyst is so large as to fill the abdomen completely up to the costal margin, the compression is not at a single point, but the ureter is flattened against the psoas muscle for some distance above the pelvic brim. The same thing is found during pregnancy. In the fifth month the ureters are dilated and show clearly down to the level of the pelvic brim. Near full term, one of two things will have happened: either compression of the ureter for some distance above the pelvic brim, or lateral displacement of the ureter so that it escapes the point where it crosses the pelvic brim. The significant resemblance between the effects on the ureter due to the presence of an ovarian cyst and of a pregnant uterus suggest clearly that mechanical pressure is an important factor in the production of the changes occurring in the urinary tract in pregnancy. Lee and Mengert (1934) argue that the dilatation caused by pregnancy disappears too quickly in the puerperium for the case to be mechanical pressure, and conclude that a disturbance of hormones peculiar to pregnancy is the important factor, but the author has found that the dilatation of the urinary tract caused by ovarian cysts in the nonpregnant disappears very quickly after removal of the cyst. Further, after pregnancy the disappearance of the dilatation is often delayed, and the finding of Lee and Mengert to the contrary is due to their reliance on intravenous pyelogra-

phy to demonstrate the contour of the urinary tract. While this method is admirable during pregnancy, the lack of obstruction to outflow makes it quite unreliable in the puerperium when recourse to retrograde pyelography is necessary.

When the cyst presses equally on both ureters, the right ureter is more dilated than the left. The preponderance of dilatation of the right urinary tract in pregnancy is probably due to the same cause.

Fibromyoma.—It has been possible to perform urological examination in only 5 cases of fibromyoma large enough to be comparable as regards size with the pregnant uterus in the second half of pregnancy. Delay in excretion was not observed in any case and when the abdomen was opened it was seen that there was no direct pressure on the ureters, as the firm consistency of the tumor prevented it from fitting closely into the irregularities of the pelvic brim. This is additional evidence of the obstruction in pregnancy occurring at the pelvic brim.

Baird states that in his survey of 28 cases of pelvic cellulitis, ovarian cyst and fibromyoma, he demonstrated conclusively that tumors of sufficient size and soft consistency can compress the ureter and cause an interference with renal function. If the cyst is situated to one side, it causes dilatation of the urinary tract on the same side and less or no dilatation on the other side. When the cyst fills the abdomen uniformly and appears to exert pressure equally on both sides, the right urinary tract is more exposed to pressure than the left. As a rule, the dilatation produced in these cases is less than that produced in a pregnancy of corresponding size, and the consequent stasis is very markedly less because the tone of the ureter, as judged by the vigor of the efflux, is not

impaired in the nonpregnant state to the same extent as in the pregnant state. It has been said in support of the statement that ovarian cysts do not cause dilatation of the urinary tract, that pyelitis is never seen in these cases, but as the incidence of clinical pyelitis, even in pregnancy, is only 1 per cent., much larger numbers would have to be studied before definite conclusions could be reached. Moreover, as in the absence of pregnancy the stasis is never so great as when pregnancy is present, the liability to infection cannot be so great.

*Incidence.*—Pyelitis is one of the most common complications of pregnancy. In a period of 2 years it was found by D. Baird (J. Obst. and Gynæc. Brit. Emp. 43:1 (Feb.) 1936) in 15.6 per cent. of all patients admitted to the antenatal wards of the Glasgow Royal Maternity and Women's Hospital. It is as common as albuminuric toxemia, contracted pelvis, and abortion. The most important predisposing factor is stasis of urine in the upper urinary tract. Stasis always precedes the onset of infection. The health of the patient is not an important factor in its development, as it occurs most typically and in its most severe form in healthy young primigravidæ. It does not appear to be associated with any particular physical type. In over 90 per cent. of the cases the infecting organism belongs to the coliform group. Urinary infection in the absence of pregnancy is also most often due to coliform organisms.

*Pathology.*—There are 3 principal routes by which infection may reach the kidney—the blood-stream, the lumen of the ureter, and the lymphatics. The majority of clinical workers in England, according to Baird (*Ibid.*), believe that the organism is absorbed from the bowel and carried to the kidneys by the blood-stream. Organisms were found in the blood in 2 cases of pyelitis of preg-

nancy. The author believes that if blood were taken for culture early enough in the disease, a positive result would be obtained, and that following intestinal disturbance organisms are absorbed into the blood-stream and thereby carried to the kidney.

In the absence of pregnancy, acute pyelonephritis is usually bilateral. Three types of lesions are found in subacute and chronic pyelonephritis:

Type 1.—The parenchyma is more involved than the renal pelvis. If the organism is of low virulence and the local resistance is good, fibrosis not unlike that occurring in nonsuppurative nephritis results.

If the fibrosis is diffuse, it will lead to atrophy of the kidney, and if it is patchy, to irregularities of the cortex due to scars and retracted areas. Secondary calculus formation is common. There is only moderate dilatation of the calyces, as usually there is no obstruction to the outflow of urine.

Type 2.—The renal pelvis is more involved than the parenchyma. In some cases there is obstruction at the ureteropelvic junction, and in others the obstruction is lower down. Changes in the wall of the pelvis of the kidney occur. There may be small nodules, due to lymphoid infiltration, metaplasia of the epithelium and leukoplakia.

Type 3.—The changes are of equal intensity in the renal pelvis and parenchyma. Destruction of the parenchyma with the formation of multiple abscess cavities occurs. There is an increase in the peripelvic fat invading the hilum and compressing the renal pelvis. The capsule of the kidney may be thickened and the perirenal fat adherent. The renal pelvis and calyces are dilated at the expense of the parenchyma. The dilatation is due either to obstruction to outflow or to atony of the wall of the

ureter and renal pelvis resulting from inflammation.

*Symptoms.*—It is customary to divide cases of pyelitis of pregnancy into 2 groups, the *acute* and the *chronic*, according to the severity of the urinary symptoms. The condition is frequently wrongly diagnosed. Of 156 cases of pyelitis of pregnancy reviewed by Baird (*Ibid.*), 98 (60.8 per cent.) were diagnosed incorrectly. In some, the error was due to the absence of symptoms referable to the urinary tract, and in others, to the fact that the symptoms were so slight that they were not recognized. The most frequent erroneous diagnosis is albuminuria, and the next most common, hyperemesis. When acute pain and tenderness are present, the diagnosis may be in doubt, as the condition may simulate pleurisy, pneumonia, or appendicitis.

In 78 of the 156 cases reviewed there was no fever. In 53 (34 per cent.), fever was present for less than one week. Of the multiparæ, 9.1 per cent., and of the primigravidæ, 27.6 per cent., had fever for from 7 to 14 days. Six primigravidæ but no multiparæ had fever for more than 3 weeks. These findings show that the disease is more serious in primigravidæ than multiparæ.

The urine practically never becomes sterile before the end of pregnancy, and exacerbations during the course of pregnancy are common.

*Diagnosis.*—The methods used to study the effect of infection on the urinary tract are chromocystoscopy, catheterization of the ureters, determination of the urea concentration of the urine of each kidney, McLean's urea estimation, and intravenous pyelography.

*Prognosis.*—In the 127 unselected cases of pyelitis treated medically in which the result was known, Baird (*Ibid.*) reported 4 maternal deaths. One of the deaths, however, was due to

cardiac disease. The mortality, therefore, was 2.3 per cent. In 192 especially selected cases there were 7 deaths, a mortality of 3.6 per cent. The stillbirth and neonatal death rate was 15.7 per cent. in the unselected cases and 19.7 per cent. in the selected cases. Of 132 primigravidæ, 4 (3 per cent.), and of 187 multiparas, 6 (3.2 per cent.) died. The stillbirth or neonatal death rate was 25.7 per cent. in the cases of primigravidæ and 14.4 per cent. in those of multiparæ.

*Treatment.*—In all cases of pyelitis treated by Baird (*Ibid.*), the patient is put to **bed** and **kept warm**, but no attempt is made to induce diaphoresis. She is confined to bed until the temperature has been settled for a week. In the acute stages, **abundant fluids** are given, at least 100 ounces in 24 hours in fairly small quantities at frequent intervals. A mixture of **potassium citrate** and **sodium bicarbonate**, 40 grains (2.6 Gm.) of each, is given every 4 hours night and day. When diuresis has been established, a nourishing light **diet** is given. **Liquid paraffin** is given to obtain easy movement of the bowels. Drastic purgatives are contraindicated. When the *pain* is severe, **morphine** is given in the acute stages and **antiphlogistine** is applied to the region of the affected kidney. If the patient becomes sick, the amount of alkali is reduced or stopped. Reduction of the alkalies often stops the vomiting as alkalies are very nauseating to some patients. When the temperature has been settled for about 10 days, **hexamine** and **acid sodium phosphate**, 10 and 15 grains (0.6 to 1 Gm.), respectively, are given 4 times a day.

There seems little doubt that the most important single essential in the treatment of pyelitis is an **abundant fluid intake**. If the fluid intake in a period of 24 hours is over 100 ounces the

acute phase of the attack usually does not last very long.

**Hexamine** liberates formaldehyde which, in a dilution of 1:20,000, allows very few organisms to grow. However, the liberation of formaldehyde is considerable only when the hydrogen-ion concentration of the urine fails to 4.

A full light diet should be given as soon as possible. Patients are too often allowed to become anemic and thin from starvation.

**Posture** undoubtedly plays a part in many cases. Most patients suffering from pyelitis prefer to lie with the thighs well flexed, as this position relaxes the psoas muscles and diminishes the compression of the ureters, thus relieving the pain to some extent.

**Ureteral catheterization** is usually held to be contraindicated in the acute stage of an infection, but as obstruction to the outflow of urine by the pregnant uterus is of such importance in the production and persistence of urinary infection, the author gave the method an extensive trial. The value of drainage by ureteral catheter is due to the relief of obstruction to the outflow of urine which it brings about.

**Renal Tuberculosis.**—In tuberculosis of the kidney, pregnancy is more than likely, as a result of increased physiological activity, to light up an old focus of disease.

**Symptoms.**—W. S. Pugh (J. Urol. 35:160 (Feb.) 1936) notes that there are no typical symptoms of tuberculosis of the kidney in pregnancy. The symptomatic peculiarities of the condition are due largely to the changes in the urinary passages taking place during gestation. In the majority of cases the first symptom is pollakiuria, usually of the painful type, which persists both during the day and at night. Pyuria is so often associated with other diseases that it is of little diagnostic aid. Hematuria is

fairly frequent and often one of the first signs noted, but must be distinguished from the hemorrhages of the bladder and urethra occurring so frequently in pregnancy. Fever is an important symptom and is particularly high, often reaching 40° C. (104° F.).

**Diagnosis.**—Pugh (*Ibid.*) states that in his experience small amounts of albumin in the urine were not significant. A clear sterile urine is far more suggestive. Tubercle bacilli are found in about one-half the cases.

The physical examination should include a study of the vagina and palpation of the ureters. If definite ureteral rigidity is found, the condition is quite certain to be tuberculosis. *Ureteral catheterization* and *pyelography* yield certain definite indications and are not contraindicated at any stage of pregnancy. Bilateral pyelography is less harmful than failure to employ it. If careful urinalysis does not demonstrate the tubercle bacillus, inoculation of a guinea-pig will usually confirm or disprove the diagnosis. A typical pyelogram in renal tuberculosis cannot be described, but the x-ray demonstration of ureteral rigidity is most certain evidence of renal tuberculosis.

**Treatment.**—The treatment of choice of unilateral tuberculosis in pregnancy is **removal of the kidney**. The so-called conservative methods should be reserved for bilateral affections and tuberculosis of a remaining kidney. The beneficial effects of **ultraviolet light** must not be overlooked in this connection.

As the renal process is acutely exacerbated in practically all cases with obstruction, the author urges immediate intervention. Interruption of the pregnancy not only fails to check the disease process, but is dangerous, particularly in the late months. It should be done only when the patient refuses nephrec-

tomy or an infection of both kidneys is present.

Pregnant women stand the operation well. As the average mortality of the children born of tuberculous mothers is about 60 per cent., early removal of the tuberculous focus appears to be indicated in the interest of the child as well as the mother.

The author regards cases of renal tuberculosis as an important field for contraception.

Five cases in which the woman went to full term and was delivered of an apparently healthy child after nephrectomy are reported. One patient died 15 months later of abdominal tuberculosis with extensive ulceration of the sigmoid flexure and perforation into the intestinal canal.

In the postoperative treatment **physiotherapy** is indispensable.

**Syphilis.**—The Coöperative Clinical Group has studied the pooled records from 5 large syphilis clinics to determine the outcome of pregnancy in treated syphilitic women. This study comprised 3817 syphilitic women under treatment or observation for 6 months or more. There were 603 women who had 922 pregnancies after their syphilitic infection. The results of 607 of these pregnancies are known and form the basis for the statements in this paper.

H. N. Cole, L. J. Usilton, J. E. Moore, P. A. O'Leary, J. H. Stokes, U. J. Wile, J. Parran, Jr., and R. A. Vonderlehr of this group (J. A. M. A. 106:464 (Feb. 8) 1936) offer the following treatment:

*Treatment of Pregnant Syphilitic Woman.*—If the diagnosis is made early, an intravenous injection of **arsphenamine** (from 0.2 to 0.4 Gm.—3 to 6 grains) or **neoarsphenamine** (from 0.3 to 0.8 Gm.—5 to 10 grains) should be given every week for from 12 to 15 weeks, followed by 10 weekly injections

of either **potassium bismuth tartrate** (0.2 Gm.—3 grains), **bismuth salicylate** (0.2 Gm.—3 grains) or **sodium potassium bismuth tartrate** suspended in oil, each dose yielding from 0.05 to 0.1 Gm. ( $\frac{3}{4}$  to  $1\frac{1}{2}$  grains) of metallic bismuth each. If possible, the schedule should be arranged to finish up with an arsenical, and treatment should be continued to term. If the diagnosis is made late in pregnancy, combined **arsenical and bismuth treatment** is indicated. Even late, inadequate treatment may mean a living, possibly nonsyphilitic child.

The data collected by this Coöperative Clinic Group show that congenital syphilis is practically a preventable disease. Its prevention is dependent on the routine, early and repeated use of the serologic blood test on every pregnant woman, and on adequate early treatment once the diagnosis of syphilis has been made.

A positive blood test during pregnancy is a serious matter to the fetus. Ten times as many syphilitic children were born when the syphilitic mother's blood was positive during pregnancy as when it was negative.

The pregnant syphilitic woman was found to tolerate antisyphilitic treatment as well as or better than the syphilitic woman who had not been pregnant since infection.

There is evidence that habitually aborting syphilitic women are capable of producing living, apparently nonsyphilitic children when given specific treatment throughout each pregnancy.

Many more nonsyphilitic living children were born when antisyphilitic treatment was begun before the fifth month of pregnancy than when therapy was delayed. This advantage was increased if the treatment during pregnancy was not only early but adequate, *i. e.*, at least 10, preferably 15 injections of arsphenamine and appropriate heavy metal.



If an early syphilis appears late in pregnancy, some treatment begun at this period and continued up to termination of pregnancy, even though it is only a small amount, will be of value in the production of a living child. To those women with early syphilis who were treated after the fifth month of pregnancy, only 7.6 per cent. of the children were born dead; whereas among a similar group of women with early syphilis to whom no treatment was administered during pregnancy, the loss of life was 46 per cent.

Treatment during a preceding pregnancy is insufficient protection for the present pregnancy, even though the syphilitic woman has a negative blood reaction. It is necessary to treat her throughout each pregnancy to insure a living nonsyphilitic infant.

The important factors in controlling clinical progression and relapse in the syphilitic woman are the stage of syphilis on beginning treatment and the amount of therapy administered, rather than the pregnancy. The possible exception is the apparent protection pregnancy affords the patient with early syphilis in avoiding an involvement of the central nervous system.

**Toxemia.**—*Symptoms.*—The ophthalmoscope, according to A. V. Hallum (J. A. M. A. 106: 1649 (May 9) 1936), should be rated next to the sphygmomanometer as an instrument of diagnostic importance in the management of a case of hypertensive toxemia of pregnancy.

Generalized narrowing and localized spastic constriction of the retinal arterioles are the earliest changes in the fundus oculi, retinal edema, hemorrhages and exudates appear later if the toxemia progresses in severity.

When hypertension develops or increases during pregnancy, careful watch should be kept for angiospastic lesions of the retinal arterioles. Pregnancy

should be terminated if the progress of these lesions cannot be controlled by conservative measures, and certainly before the onset of retinitis.

The arterioles may regain their normal caliber if there is a sufficiently early reduction of the blood-pressure to normal.

The author has found that if retinitis occurs before the twenty-eighth week of pregnancy, there is only about a 25 per cent. chance of the patient giving birth to a living child, even if pregnancy is continued to the stage of viability, and there is almost 100 per cent. chance of permanent vascular-renal injury developing. If toxemia precedes the twenty-eighth week of pregnancy and is not accompanied by retinitis, the prognosis is slightly better.

*Retinal detachment* occurs in about 2 per cent. of hypertensive toxemias of pregnancy. The detachments usually become reattached within 10 days after termination of the pregnancy.

From May, 1931, to March, 1936, 1018 cases of toxemia of pregnancy were delivered in the Department of Obstetrics and Gynecology of the University of Chicago at the Chicago Lying-In Hospital. Among these patients there have been 26 cases showing a drop in systolic *blood-pressure* of more than 70 mm. of mercury. There were profound clinical manifestations of shock in addition to the fall in blood-pressure in 16 of these cases, 11 of which were of the chronic and 5 of the acute type. Energetic treatment followed the occurrence of collapse in all, and yet 4 patients relapsed into shock a second time and required repetition of the treatment.

Parturitional vascular collapse is a grave condition occurring typically in a rather small percentage of elderly multiparae who have been afflicted with a progressively severe nephritis in succeeding pregnancies. The incidence of

this condition in this clinic, as reported by F. L. Adair, A. B. Hunt and R. E. Arnell (J. A. M. A. 107:1036 (Sept. 26, 1916), was 0.2 per cent. of all deliveries and 2.55 per cent. of all toxemic patients.

The toxemia seems to be the most important etiologic factor, with delivery definitely exciting the appearance of vascular collapse.

The blood-pressure and general condition of cases of severe and chronic toxemia should be watched closely for 12 hours after delivery. Equipment and personnel should be ready for prompt and effective treatment in the event of the collapse of such a patient.

The mortality is high, 15.49 per cent. of 71 cases reported. The condition is an entity deserving of recognition and further study because of its gravity and because proper treatment should reduce the mortality appreciably.

The most common pathologic lesion was a chronic glomerulonephritis.

*Treatment.*—In treatment of these patients, Adair, Hunt and Arnell (*Ibid.*) recommend that the blood-pressure and pulse be watched closely for several hours after delivery. A **tight binder** and a small **sand bag** applied to the **abdomen** may compensate for the pressure of the previously gravid uterus and prevent a collapse.

Prompt treatment, in the event of a collapse of the blood-pressure, will be required to save the patient if the systolic pressure remains below 60 mm. of mercury for any length of time. The obstetrician should not wait for this to occur. Prolonged anoxemia is followed by a severe acidosis and irreparable damage to the brain. Hypertonic intravenous **dextrose** of 20 per cent., and occasionally 30 per cent., is the best agent to raise the blood-pressure. **Acacia**, 30 Gm. (1 ounce), with 4.5 Gm. ( $67\frac{1}{2}$  grains) of **sodium chloride** in

100 c.c. ( $3\frac{1}{2}$  ounces) ampoules diluted to 500 c.c. (1 pint) with freshly distilled water, given intravenously, is useful. A hypodermoclysis of not too great an amount may be started early, but isotonic dextrose rather than sodium chloride should be used in these patients. **Blood transfusion** may be needed, as the serum proteins exert a more prolonged osmotic effect to pull and hold fluids in circulation.

Hypodermic use of **ephedrine** and solution of **posterior pituitary** is indicated. The usual treatment of shock from any cause is always in order, such as the steep **Trendelenburg position**, **external dry heat**, **caffeine** by hypodermic injection or a **hot coffee enema**. Even **binding** the **extremities** toward the torso may be of aid in an emergency. A functional cerebral blood circulation must be maintained.

When the diagnosis is made, the administration of **dextrose** should be started immediately and if the collapse is profound from 2 to 3 minims (0.12 to 0.18 c.c.) of 1:1000 **epinephrine** should be injected by hypodermic syringe into the tubing near the vein and the remainder of the 1 c.c. ampoule be emptied into the dextrose flask.

After the initial recovery, the patient must be watched for several hours for detection and treatment of a relapse.

The urinary output is an important guide to *prognosis*, especially as a *partial anuria* is a secondary danger that the patient faces after recovery from the initial collapse. If this occurs, the hypertonic **dextrose solution** may need to be increased from 20 to 30 per cent., or even to 50 per cent., to obtain a satisfactory urinary output.

**DIAGNOSIS.**—*Intradermal Test.*—B. Gruskin (Am. J. Surg. 31:59 (Jan.) 1936) bases his test on previous work concerning the nature of homologous proteins producing an allergic re-

action by the formation of pseudopods when injected intradermally in positive cases of malignant manifestations. The same principle has been applied in the determination of pregnancy by the use of *placental tissue* as an antigen, which, when introduced intradermally, causes pseudopod formation at the site of injection in pregnant women, but no pseudopods appear when pregnancy does not exist.

One-tenth cubic centimeter of the antigen is injected intradermally with a 27-gauge needle and a 1 c.c. tuberculin syringe. The injection should not be forced. In positive cases a slight area of inflammation with pseudopod formation appears within 10 minutes. In negative cases no such reaction takes place. It is advisable to use a control of physiologic solution of sodium chloride with each test. The control must always be negative, showing no inflammation and no pseudopods. The bleb after the injection must be perfectly round and have the appearance of orange peel, due to the hair follicles, in which case there is the certainty that the test was done intradermally.

For the *preparation of the antigen*, placentas are obtained as soon as possible following delivery. They are washed, cleansed and freed from blood, ground into pulp and placed in acetone, 3 times their volume, for 24 hours. The acetone is poured off, the tissue allowed to dry, and the acetone evaporated. It is then extracted with 0.1 normal sodium hydroxide solution for 24 hours and neutralized with a solution of hydrochloric acid and a buffer solution made of 0.05 normal hydrochloric acid and 2.27 Gm. of potassium dihydrogen phosphate per liter. The antigen is brought to a pH of 6.9, and 6 drops (0.4 c.c.) of a mixture of 2 parts of glycerin to 1 of tricresol for every 10 c.c. of the extract is added as a preservative. It is then placed in pyrex containers and is ready for use.

This test should not be done during menstruation, owing to the decidual involvement of that process which will respond to the homologous protein of the placental extract, giving positive reactions. It should not be performed in endocrine disturbances or on hypersensitive skins, which might respond to anything.

An intradermal skin test for pregnancy, employing *anterior pituitary-like sex hormone*, is described by G. C. Gilfillen and W. K. Gregg (Am. J. Obst. and Gynec. 32: 498 (Sept.) 1936). This test is based upon the thought that if a pregnant woman has this substance in her system, she might not be sensitive to its intradermal application, and, on the other hand, a nonpregnant woman might show a reaction to its presence.

The test consists of an intradermal injection of 2 minims (0.12 c.c.) of fresh antuitrin-S which has been kept in an ice-box. The ventral surface of either forearm is the site of the injection. An ordinary 2 c.c. hypodermic syringe and 26-gauge needle is used for the intradermal injections. It is important that the skin, syringe, and needle be cleansed with sterile water and not alcohol, as alcohol reduces the potency of the antuitrin. It is also important that a true intradermal injection be made, as deeper injections are not satisfactory.

After introducing 2 minims (0.12 c.c.) intradermally, one-half hour is allowed to elapse before reading the reaction. If there is a slight reaction, the authors wait another one-half hour before drawing their conclusions. If there is no reaction at the end of this time, they do not observe the patient longer. Patients 30 years or older delayed the reaction for a longer period, and those near the menopause reacted as late as 3 hours. If there is a reaction, it is best observed at the end of 2 hours. It consists of an area of erythema around the site of injection measuring in diameter from 7 to 35 or 40 mm. Occasionally a reaction will reach 5 cm., but usually the area of erythema will measure 25 to 30 mm. If the bleb which is raised by the injection into the skin becomes red, but the skin adjacent and surrounding the bleb does not become red, then this is not a positive reaction. The reddened area overlying the bleb will measure 7 mm. or less. Obviously, a negative test is one in which there is no erythema surrounding the point of injection except, as noted above, that which overlies the bleb and measures 7 mm. or less.

A patient who is pregnant or who has aborted and retains some live decidual cells, does not react to the antuitrin-S. A patient who is not pregnant nor has any retained living tissue of the products

on the uppermost part of the head in breech presentation. The character or strength of the tissue put under stress is an important determining factor.

Bearing these points in mind, C. E. Galloway (J. A. M. A. 106: 505 (Feb. 15) 1936) warns that nothing should be done to hasten delivery until the head is visible or on the pelvic floor. The use of solution of posterior pituitary and other drugs to cause more rapid descent of the head is contraindicated.

**Episiotomy** is indicated in order to relieve pressure as the head comes through the narrow vaginal opening, especially in cases in which the baby is premature.

Premature rupture of the membrane, either for induction or to hasten labor, seems contraindicated because of the negative pressure exerted on the presenting part.

**Outlet forceps** in conjunction with **episiotomy** will probably result in fewer cerebral hemorrhages. If forceps are used, it is much less dangerous to make a cephalic application than a pelvic application and it is also quite essential that there be no squeezing with the blades.

Many obstetricians as a routine procedure give the baby an **injection of 20 c.c. of whole blood in the thigh** following all difficult deliveries.

Another *contributing cause*, and one that is probably considered by most men, is a too prolonged test of labor. Since **Cesarean section** now carries a satisfactory low risk, it behooves the obstetrician to use it oftener in cases in which the pelvis is known to be abnormally flat or small rather than to allow the baby to develop a cerebral hemorrhage in an attempt to see whether the uterine contractions can force the head through the inlet.

**B. Brachial Palsy.**—Injury to the brachial plexus is generally due to

stretching of the first and sixth cervical nerves and nerve roots. The obstetrician should use as little force as possible on the head in vertex presentations and in such an event **light anesthesia** seems indicated, as the uterine contraction will be more likely to deliver the shoulder.

**Dropping the end of the bed** and **Kristeller expression** are both useful maneuvers *in delivering the shoulders*. Sharp angulation of the spine in breech contributes to this injury, and the pressure of the fingers on the neck and shoulders of the baby during breech extraction is one of the most common causes.

**C. Fractured Clavicle.**—The operator should avoid traction on the head or neck. In vertex presentation the finger should reach for the axilla as soon as possible, and **light** rather than **deep anesthesia** seems indicated.

**D. Facial Paralysis.**—Facial paralysis occurs most often in forceps delivery, owing to the pressure of the blades on the tissues surrounding the facial nerve. It may be central, however, because either of cortical or of intramedullary hemorrhage. It has also occurred in spontaneous delivery, especially when there was a flat or contracted pelvis. Unless central in origin, the paralysis disappears in from a few minutes to a few days.

**E. Breech Delivery.**—Breech extraction calls for **complete dilatation** and **deep ether anesthesia**.

During breech extraction the operator should avoid pressure on the fundus, extreme angulation, excessive suprapubic pressure and dangerous traction. It is possible to elongate the spinal column about 5 cm., and the thoracic cord of the fetus is only about  $\frac{1}{8}$  inch (0.3 cm.) in diameter. The cord is enlarged in the cervical and lumbar region and is well anchored by the brachial plexus above and the cauda equina below. It is for

these reasons the authors state that extreme traction causes thoracic cord injury in some cases.

**Breech Presentation.**—T. R. Goethals (Surg. Gynec. and Obst. 62:525 (Mar.) 1936) presents a review of 1242 breech deliveries in the Boston Lying-In Hospital during a period of 20 years. The gross combined fetal (stillbirth) and neonatal death rate was 25.7 per cent. In 272 deliveries either the pregnancy was pathologic, with such complications as preëclamptic toxemia, eclampsia, nephritis, syphilis, diabetes and hydramnios; or labor was complicated by such conditions as placenta previa, ablatio placentæ or prolapse of the cord. Since the crude mortality in this group was 51.8 per cent., the effect of pathologic pregnancy and labor as an important factor in the high gross mortality was 18.5 per cent. Prematurity of the infant was common in both groups and contributed in no small measure to the crude mortality in each. Uncomplicated deliveries produced premature infants in 15.7 per cent. of the cases, with a crude mortality rate of 62.1 per cent.; pathologic pregnancies and labors resulted in the birth of 43.3 per cent. of premature infants, with a crude mortality rate of 82.2 per cent. The risk of breech delivery alone should be computed only from cases in which uncomplicated labor occurs.

This series shows the incidence of placenta previa, ablatio placentæ and prolapse of the cord to be respectively 3, 5, and 5 times as frequently associated with breech presentation as with all types of delivery. In uncomplicated breech delivery the crude mortality resulting from primiparous single pregnancy was 18.1 per cent.; from multiparous single, 17.2 per cent.; from primiparous multiple, 24.3 per cent., and from multiparous multiple, 23.8 per cent. In correcting the crude mortality figures

in this series, the only cases excluded are those resulting in the birth of macerated infants and grossly malformed babies. Using this standard for uncomplicated breech delivery, the corrected mortality was 13.6 per cent. among 916 newborn infants, subdivided as follows: 53.6 per cent. for premature, 10 per cent. for immature, and 6.9 per cent. for mature infants. The mortality figure of 6.9 per cent., therefore, represents the risk to the living, undeformed, full term infant *in utero* who is destined to be born by pelvic breech delivery in the absence of pathologic pregnancy on the part of the mother, and of hemorrhagic and other accidents of labor due to abnormalities of the placenta or of the umbilical cord.

**Hemorrhage.**—*Treatment.*—The low blood-pressure and the rapid pulse subsequent to delivery can be temporarily, at least, successfully combated by the intravenous injection of dextrose. In cases of hypotension, H. B. Matthews and V. P. Mazzola (Surg. Gynec. and Obst. 62:781 (May) 1936) advise the use of intravenous 50 per cent. solution of dextrose to give the patient a wider margin of safety. Cases of acute hemorrhage with diminished blood-pressure have shown increase in blood-pressure by the intravenous injection of 100 c.c. of the solution. It tides these patients over until blood transfusion can be started. In primary shock or collapse, it increases systolic blood-pressure and greatly aids in bringing the circulation back. Preoperative dextrose makes reduction of blood-pressure from hemorrhage or prolonged surgery more difficult. After operation it aids in overcoming acidosis and dehydration. By its action on the circulation, physiologic solution of sodium chloride administered by hypodermoclysis is more readily absorbed. It also aids in supplying carbo-

hydrates when the oral route is contraindicated.

In *shock*, with or without hemorrhage, the dextrose solution is to be commended. Active treatment must be instituted before there is complete circulatory collapse. The patient who receives prompt treatment is the one who recovers. When blood is not available or when time is pressing, concentrated dextrose solution makes an excellent substitute. Concentrated dextrose preoperatively maintains pulse pressure, causes a slight rise in systolic blood-pressure and, if repeated, prevents a fall. It diminishes postoperative vomiting and has considerable value as a food in the presence of peritoneal infection. Little or no damage is done the vein by its injection, provided the intima of the vessel is not excessively traumatized.

**Lacerations.—Treatment.—Immediate Repair.**—For the management of cervical lacerations following childbirth various plans have been proposed. W. C. Danforth (Am. J. Obst. and Gynec. 32: 710 (Oct.) 1936) claims that immediate repair is preferable to suture done later during the puerperium, on the fifth or the tenth day. It is true that immediately after labor the cervix is soft, but due attention to technic is followed by results sufficiently satisfactory to make the plan worth while. In some instances a notch in the cervix may indicate the location of the tear at the end of the puerperium. If the major portion of a deep injury may be made to heal, the resulting ectropion is reduced or prevented.

In order to obtain healing which is satisfactory a rather definite plan must be followed, the essential points of which are described by the author. DeLee, some years ago, pointed out and Danforth confirmed his observation by the examination of many lacerated cervixes, that the muscular structure of the in-

jured cervix retracts so that the cross-section of the torn edge of the cervix forms a "V," the two arms of the "V" being the mucosa of the cervical canal and the vaginal surface of the cervix, respectively. The sutures then must go sufficiently deep to grasp the retracted muscle. If the suture passes only through the arms of the "V," or the edges of the mucosa, it will inevitably cut through. The operator must sacrifice to a certain extent the desire to make an extremely neat suture line and place the suture deeply enough to grasp the muscular portion of the cervix. As the tissues grasped by the suture are very soft, they must be tied with but little force. In the presence of an abundant blood supply, healing is rapid. Suture material of long life is, therefore, not needed. Care must be exercised during the placing of sutures that too much traction is not put upon the cervical lips in the desire to obtain good exposure. It is easy to stretch them or to elongate one more than the other, thus causing an uneven approximation.

**Intermediate Repair.**—A plea for the intermediate repair of injuries resulting from childbirth is offered by S. E. Tracy (*Ibid.* 31:333 (Feb.) 1936). In many cases it is impossible immediately after delivery to determine whether a laceration of the cervix uteri is present and its extent. If present, its repair is not especially easy. For this reason most obstetricians are content to place a few stitches in a plainly visible midline laceration of the perineum, and leave other injuries to the tender mercies of nature. Such a procedure will restore the genital canal to a normal condition in but a small percentage of patients. If immediate repair of the cervix and perineum is attempted, it is difficult to evaluate the full extent of the injury.

If those who favor immediate repair will, for the time being, disregard the

visible perineal lacerations and examine the patients from 5 to 7 days after delivery, they will be surprised to note how many have lacerations of the cervix uteri with no evidence of spontaneous union; that many lacerations of the perineum which at the time of delivery seemed simple and superficial, are in reality deep and extensive; that lacerations which were overlooked, extend through the vaginal walls and levator ani muscles high up at the side of the vagina; and that submucous separation of the muscles in the perineum and of the supporting tissues under the bladder which were not suspected, exist in a considerable proportion of these women.

The ideal *time to do this repair work* is after the tissues have recovered from the trauma of labor, usually from 5 to 10 days after delivery. Tracy feels that no patient should be discharged with any of the possible enumerated lacerations to suffer discomforts from scar tissue and from loss of pelvic support, when by intermediate repair the genital canal can be restored to a normal condition, and the patient enjoy the same health as before conception took place. The economic and sociologic advantage gained by these patients in one rather than two hospital sojourns, is incalculable.

The *advantages* of intermediate repair of these lacerations are manifold. The true extent of the damage to the pelvic structures can be determined more accurately at this time; all lacerations, wherever located, can be sutured and the result of the operation on the perineum will be decidedly better than after the immediate operation.

If the patient has had a normal convalescence, intermediate repair is usually performed on the fifth day. In the presence of morbidity, the operation is not attempted. The *day before the operation* the bowels are emptied well by a **cathartic**, and on the day of the

operation by an **enema**. The patient is given no breakfast in the morning. She nurses her baby that morning as usual. **Ethylene gas** is preferred, as it does not interfere with lactation. After the patient is anesthetized, the preparation of the pelvic field is the same as for a secondary operation.

In doing intermediate repairs no predetermined operation can be carried out. The damaged structures, wherever located, are repaired; the object being complete restoration of the parts to a normal condition.

*Technic.*—The first procedure is to dilate the cervix uteri. Any retained detritus is removed with long loop forceps, and the endometrial cavity is dried with gauze. It is surprising how frequently a portion of membrane or a retained piece of placental tissue is found, which is one explanation of vaginal bleeding for several weeks after delivery.

The irregular edges of the cervical laceration are then trimmed and the granulation tissues removed. Interrupted chromic catgut sutures are introduced with a noncutting edge needle. A generous os, at least 1.5 cm., should be provided to allow for involution. Following this, any damage to the anterior vaginal wall is repaired as in a secondary operation. The tissues are approximated with interrupted sutures.

The irregular edges of the wounds in the vaginal canal and in the perineum are then trimmed, and the granulation tissue scraped away so that the surfaces will be fresh and healthy. The wounds are then accurately approximated with interrupted sutures. Below the level of the hymen the tissues in the perineum are approximated by two layers of interrupted sutures.

It is most important to close the upper angles of the wounds so that the tissues will not be undermined by the lochia. The sutures should not be drawn tighter than is sufficient to coapt the tissues.

**Placenta Previa.**—*Diagnosis.*—F. J. Burke (J. Obst. and Gynæc. Brit. Emp. 42:1096 (Dec.) 1935) points out that placenta previa can be diagnosed by *amniography*. The most characteristic radiographic appearances of the placenta

*in utero* are obtained when the placenta occupies the lower uterine segment. There are a number of factors that materially influence the success of the investigation. Obesity of the patient will defeat the most enthusiastic investigator. As the placenta cannot be seen unless it is viewed in profile, more than ordinary care is necessary in conducting the x-ray examination. The amount of amniotic fluid has an important bearing on the result. If there is an excess, the density of the shadow produced by the contrast medium may be insufficient for diagnostic purposes, and, unfortunately, there is no rapid method by which the amount of amniotic fluid can be estimated. On the other hand, if the fluid is scanty in amount, uterine puncture may be unsuccessful. This probably is the most serious obstacle in amniography, and in a certain percentage of cases it cannot be performed. In most cases amniography is unnecessary, yet a marginal placenta previa, which may prove fatal, may at an early stage be indistinguishable from a mild accidental hemorrhage. Amniography in all cases of ante partum hemorrhage does not seem practical, nor is it likely to be profitable.

The *indications* for amniography may perhaps be defined by stating that if in a doubtful case of placenta previa the history of the case, the physical signs and other important considerations, *e. g.*, age of the patient, parity, or desire for a live child, are sufficient to indicate Cesarean section as a possible mode of delivery, amniography should be performed. But if delivery will be natural in any case, there is little or nothing to be gained by subjecting the patient to the examination.

The main *value* of amniography appears to be as a deciding factor for or against delivery by Cesarean section. There is a definite place, therefore, for amniography in ante partum investiga-

tion. The placenta is actually visualized so that there is no difficulty in deciding whether the placenta previa is central, marginal or lateral in type. With such accurate information, and having due regard to other circumstances, the mode of delivery should no longer be in doubt. If the diagnosis proves to be one of central placenta previa, Cesarean section can be undertaken with beneficial results to the child and in full confidence that the mother is not being exposed to unnecessary risk. If lateral placenta previa is diagnosed, natural delivery can be awaited without undue apprehension for the safety of the mother or the child.

*Treatment.* — Obstetricians have become mortality-conscious, partly through their own efforts and partly through the efforts of an ever increasing interest in maternal mortality by the lay public.

An ever increasing number of patients with placenta previa is referred to hospitals, so that the incidence in hospital practice has been increasing and is much higher than in the general population.

Placenta previa is associated chiefly with multiparity, becoming more common with increasing parity. Recent statistical studies tend to indicate that the condition is at present only twice as common in multipara as in the primipara.

The treatment of placenta previa must be aimed at the following principles, according to M. E. Davis (*Am. J. Obst. and Gynec.* 32: 518 (Sept.) 1936): (*a*) The bleeding must be arrested; (*b*) the pregnancy must be terminated; (*c*) infection must be guarded against; (*d*) trauma must be avoided; and (*e*) the patient's general condition must be maintained. The method or methods that can accomplish these results with the lowest mortality for the mother and her child should be regarded as the procedures of choice.

The ideal management of placenta previa should begin in the prenatal



period. The patient's history should include information concerning any hemorrhage in previous pregnancies. The patient should have a careful blood study. Anemic patients should receive adequate therapy during the pregnancy for the restoration of the normal blood picture. There has been an increase in the anemias of pregnancy during the last economic depression. Patients with a very low hemoglobin should be transfused before delivery.

Bleeding during pregnancy at any time must be considered abnormal and of sufficient importance to warrant investigation. Patients must be taught to report any bleeding occurring during gestation. When the bleeding occurs during the last trimester of pregnancy, it should be regarded of sufficient import to merit an examination, in a hospital if possible. In the literature which has been reviewed several impressions stand out vividly. In the first place, placenta previa is a complication necessitating **hospitalization**. Only under unusual circumstances is it justifiable to treat a patient in the home. In the second place, women should be referred to a hospital with their initial bleeding without manipulation in the home. To obtain any improvement in present results, these two fundamental principles must be observed.

The patient, on entering the hospital, should have her blood group determined and the blood should be cross-matched with that of a suitable donor. Examination of all kinds are usually postponed until a donor is available, for once an examination is made, the appropriate therapy must be instituted. The patient who has lost considerable blood and shows the general effects of the blood loss should have a preparatory **transfusion**.

The treatment instituted will depend on the many factors previously discussed. *Marginal placenta previa* and *partial placenta previa* in multiparas in good

condition can best be treated by simple **rupture of the membranes**. Where this does not control the bleeding, one of two procedures can be instituted: **Braxton Hick's version** or **metreuryesis**. Where the fetus is previable, a careful Braxton Hick's version is probably the treatment of choice, although its performance may be difficult. The use of **Willett's method** should be considered. The careful intraovular introduction of a suitable **bag**, large enough to provide sufficient dilatation on its passage, is preferable where the fetus is viable. It is probably a more simple procedure than Braxton Hick's version but demands more careful and intelligent observation for a satisfactory result. Following the passage of the bag through the cervix, a spontaneous delivery can be awaited if there is no bleeding, or delivery can be accomplished by **version and extraction**, or when the head is engaged, by **forceps**.

The management of the *third stage* of labor is worthy of some comment. Following the delivery of the baby, normal separation of the placenta can be awaited unless *bleeding* occurs. In that event, careful **manual removal** is indicated. In the event a difficult operative procedure has taken place, a careful examination of the entire lower uterine segment and inspection of the cervix for lacerations should be instituted. **Lacerations** which cause bleeding should be **repaired**. Atony of the uterus following placental expulsion necessitates careful exploration of the uterine cavity, evacuation of clots, and oxytocic drugs. If the bleeding continues, the uterine cavity should be firmly packed, **packing** the corporeal cavity first and then the stretched, traumatized, bleeding lower segment, and finally the entire vagina. An insecure or improperly placed pack is worse than none at all, for it acts as a plug behind

which bleeding continues. It is good practice to administer **pituitary extract** intramuscularly or better still, **ergonovine** intravenously, just as the baby is being delivered, thereby hastening the third stage.

**Cesarean section** should be reserved for the patient with total placenta previa; in the partial placenta previa when the placenta covers a considerable portion of the cervical os and the patient is a primipara; any patient that enters the hospital exsanguinated and in critical condition; where some other indication than the placental location exists, such as a borderline pelvis or an elderly primipara. The low or cervical Cesarean is probably the preferable procedure unless the placenta is palpated during operation on the anterior wall, then the low classic is probably the simpler procedure. Porro Cesarean should be considered in early multiparas with partial or total placenta previa, who are grossly infected due to previous manipulation.

The author emphasizes that measures for combating blood loss are a most essential part of any treatment of hemorrhage in pregnancy. The subsequent maternal mortality, serious puerperal infection and prolonged convalescence and invalidism can be greatly reduced by a serious attempt to restore in some measure the blood loss of the patient. For maintaining blood volume, **saline** or **Ringer's solution** can be given by hypodermoclysis, using 16-gauge needles. **Glucose solution** in 20 per cent. concentration should be given intravenously at as slow a rate as possible, discontinuing its administration just as soon as blood is available. No more than 500 c.c. should be given unless a liberal blood transfusion follows. It must be remembered that large amounts of hypertonic glucose solution draw liberally on the fluids in the tissues and increase blood coagulation time. In the event that

blood is not immediately available, 500 to 1000 c.c. of 6 per cent. **acacia** can be slowly administered intravenously. Although the blood volume be restored, sufficient circulating hemoglobin must be present to carry on the vital functions of life. The amount of the **transfusions** should depend on the blood loss, averaging 600 to 800 c.c. in the usual case.

When the treatment consisted of rupture of the membranes, the gross fetal mortality was 33 per cent.; metrorrhysis, 50 per cent.; Braxton Hick's version, where the infant must of necessity be disregarded, 54 per cent.; in Cesarean section, 12 per cent. Thus, it will be observed that Cesarean section safeguards the interest of the baby the most. By this method many babies at the borderline of viability are delivered uninjured and take up a normal extra-uterine life.

**Premature Rupture of Membrane.**—E. Essen-Möller (Acta obst. et gynec. Scandinav. 16:1 1936) compares 1000 cases of premature rupture and 300 cases of artificial rupture of the membranes. His findings are summarized as follows:

*Premature Spontaneous Rupture:*

1. Premature spontaneous rupture of the membranes is more frequent in pluriparæ than in primiparæ.
2. After its occurrence, labor is shorter in the cases of both primiparæ and pluriparæ than labor in general.
3. The incidence of infection after its occurrence is no higher than the incidence of infection in labors in general.
4. When infection develops after premature spontaneous rupture of the membranes, fever is more frequent after interventions than after spontaneous delivery.
5. The frequency of interventions is greater in cases of premature spontane-

ous rupture of the membranes than in deliveries in general.

6. The maternal and the infant mortality are no greater than after deliveries in general.

7. The incidence of prolapse of the umbilical cord is no greater than in labors in general.

*Premature Artificial Rupture:*

1. After artificial rupture of the membranes the incidence of infection is greater than after spontaneous rupture and after labors in general.

2. The frequency of interventions is greater than in labors in general, especially in the cases of primiparæ.

3. The maternal and infant mortality is higher than after spontaneous rupture of the membranes and in labors in general. To a great degree this fact is due to the condition of the mother which necessitated the intervention and to the prematurity of the infant at the time of the intervention.

It is evident, therefore, that the old fear of premature rupture of the membranes is not justified. However, it must be emphasized that premature rupture of the membranes, especially if it is brought about artificially, may be followed by serious consequences for the mother and child in a certain number of cases. Therefore, artificial rupture should be done only when it is definitely indicated. The routine use of this procedure to hasten labor, which is recommended quite frequently in present-day obstetrical literature, is to be rejected.

**OXYTICS IN OBSTETRICS.**

—M. E. Davis, F. L. Adair and S. Pearl (J. A. M. A. 107:261 (July 25) 1936) discuss the present status of oxytics in obstetrics.

*Ergonovine.*—Following a long series of investigations, Davis, Adair, Rogers, Kharasch and Legault announced in 1934 that they had succeeded in isolating and testing clinically a pure, crystal-

line base from the crude extract, which further study proved to contain most of the desirable oxytocic activity. These independent groups assigned different names to this new ergot base. The Council on Pharmacy and Chemistry of the American Medical Association has renamed this new substance ergonovine.

Ergonovine is the only alkaloid of ergot which is effective by oral administration in small doses. When administered in doses of from 0.2 to 0.4 mg. ( $\frac{1}{300}$  to  $\frac{1}{150}$  grain) by mouth, it causes a typical ergot response in 6 or 8 minutes. The uterus develops tonicity and following the initial tetany, which lasts 5 or 6 minutes, uterine motility is established which becomes more vigorous in character as the uterine tone diminishes. Good uterine motility continues for at least 2 hours and often longer, so that frequent administration of the drug is not necessary. Intravenous administration in doses of 0.2 mg. ( $\frac{1}{300}$  grain) produces an immediate response, particularly marked by the high degree of tone, which is of great importance in its therapeutic application.

The drug does not affect pulse, blood-pressure, or urinary output. Its toxicity is extremely low, so that many times the therapeutic dose causes no undesirable symptoms. The crystals are entirely stable, so that oral tablets may be kept indefinitely. The aqueous solution, however, is as yet not sufficiently stable. The powder is, therefore, best dissolved in water just before it is to be administered intravenously.

*Solution of Posterior Pituitary.*—The action of posterior pituitary extract in the immediate post partum period and in the puerperium is quite uniform. The action of the drug lasts for 5 or 10 minutes and rapidly disappears, to be reinitiated by another dose. The intravenous administration of small doses, 3 minims (0.2 c.c.), provokes an imme-

diate response. However, the general reaction to this mode of therapy is quite marked. The patient may develop a marked circumoral pallor, a sense of constriction in the chest, pain in the back of the head, marked palpitation, nausea and occasionally vomiting. The reaction may last several minutes or longer and gradually disappear without any serious effects.

Posterior pituitary extract has a variable effect on blood-pressure of normal individuals. Usually, little or no elevation of blood-pressure is observed after therapeutic doses of posterior pituitary. However, in patients with hypertension a marked elevation occurs after intravenous or intramuscular administration of the drug. The rise in pressure is transitory and is followed by a return to normal.

**Quinine.**—This is an alkaloid, derived from cinchona bark, which has maintained a wide clinical popularity. It has been used to augment weak, ineffective labor pains, but has more commonly been employed in conjunction with castor oil for the induction of labor. Its oxytocic action is very mild and unreliable, even though it is administered in doses large enough to evoke a general reaction. It is the impression of these investigators that quinine does seem to sensitize the pregnant uterus at or near term, so that it becomes more responsive to the more potent oxytocics, *i. e.*, posterior pituitary extract and ergonovine.

It has been the authors' practice to prescribe **ergot** in the puerperium for *delayed involution*. At present, **ergonovine maleate** from 0.2 to 0.4 mg. ( $\frac{1}{300}$  to  $\frac{1}{150}$  grain), 3 times daily, is given to patients who have had a post partum hemorrhage, a difficult forceps, intra-uterine manipulation, abnormal lochia, fever regardless of the cause, or delayed involution without cause. This therapy

is kept up for at least 3 days or as long as is necessary. If uterine contractions become too painful, the dose of ergonovine maleate is reduced or the drug omitted.

**LACTATION.**—*Effect of Camphor-in-Oil on.*—The effect of camphor on the breasts was first noted clinically in 1922 by J. Rosenblatt, who observed that when camphor was given to nursing mothers for cardiac disorders, it caused a reduction in the excretion of milk and within a few days produced complete cessation of lactation.

The following procedure was adopted by M. D. Klein (Am. J. Obst. and Gynec. 31:894 (May) 1936) in a study of 90 patients. Two doses of camphor-in-oil,  $1\frac{1}{2}$  grains (0.1 Gm.) each, were given intramuscularly (into the buttocks) the first day (in morning and afternoon). One injection of  $1\frac{1}{2}$  grains (0.1 Gm.) was then given daily for 3 successive days, making a total of 5 injections. The use of cathartics, ice-bags, avoided, except in the few cases where it was obvious that therapy failed. All breasts were examined every 12 hours for the first 48 hours, every 6 hours for 2 days, and daily thereafter.

It was found necessary to differentiate the reactions in the breasts into the 3 following degrees:

**First Degree.**—The breasts showed absent or slight filling and were symptom-free.

**Second Degree.**—Breasts showed moderate fullness accompanied by slight pain and tenderness.

**Third Degree.**—Breasts revealed marked fullness (even to the extent of caking) and secretion associated with severe pain and tenderness.

When given within 24 hours after delivery, 80 per cent. of the patients

failed to develop breast engorgement. When given after 24 hours and before engorgement developed beyond the first degree stage, inhibition took effect within 6 hours and the breasts returned to the normal state shortly thereafter.

When the breasts exhibited a second degree reaction before treatment was instituted, the use of camphor-in-oil prevented extension of engorgement to the third degree stage. When camphor-in-oil was given after the breasts reach the second or third degree reaction, the duration of breast engorgement was shortened to 12 hours instead of 36 hours. Furthermore, regression to the nonlactating phase was complete within 2 to 3 days instead of the usual 4 to 5 days. It is evident, therefore, that the earlier the injections are started, the less the degree and duration of the engorgement, and the quicker the breasts return to their dry state.

Fifty additional patients have been given larger doses of camphor-in-oil (3 grains—0.2 Gm.—twice during first day) with results that seem to be more effective in prevention of lactation.

**PUERPERIUM.—PUERPERAL INFECTION.—Incidence.**—The incidence of puerperal infection, according to C. H. Peckham (*Am. J. Obst. and Gynec.* 31:435 (Mar.) 1936), was almost twice as high in colored patients as in white patients, being 20.24 per cent. in the former and 11.05 per cent. in the latter.

The incidence of puerperal fever due to intrauterine infection was  $2\frac{1}{2}$  times as great in cases of operative delivery (30.86 per cent.) as in cases of spontaneous delivery (12.26 per cent.). Even a perineal tear or episiotomy with immediate repair caused a definite increase. The puerperium was febrile in almost two-thirds of the cases in which manual removal of the placenta was necessary.

In general, the risk of puerperal infection in the operative cases seemed to be in direct proportion to the amount of intrauterine manipulation.

The incidence of puerperal fever increased directly with the duration of labor, and the rate of increase was most rapid when the labor was prolonged. The average length of labor in the cases in which infection developed was  $3\frac{1}{2}$  hours longer than in the cases in which the puerperium was normal.

In the cases of women admitted to the hospital after the failure of attempts at delivery in their homes, the incidence of puerperal infection was 61.54 per cent.

The incidence of puerperal fever was lowest in the cases in which the membranes ruptured spontaneously or were ruptured artificially prior to the onset of labor, but was only 1 per cent. higher when rupture occurred during the second stage of labor. The results were most satisfactory when rupture took place during the first stage of labor.

In the presence of most medical and obstetrical abnormalities, the incidence of infection was increased. To a great extent, the increase paralleled the high incidence of operative delivery due to the complications. It appears that excessive blood loss either before or after delivery increases the incidence of infection by lowering the general resistance.

In a further study, C. H. Peckham (*Ibid.* 31:582 (Apr.) 1936) found that the incidence of operative delivery was much higher in the group of cases with puerperal infection than in the cases with a normal puerperium. Puerperal infection occurred much more frequently in colored than in white women, and the difference was significantly greater with spontaneous than with operative delivery. Women in the earlier years of their childbearing careers and primi-

paræ were more predisposed to intra-uterine infection than women of the older age groups and multiparæ. The time of admission to the hospital in terms of duration of labor seemed to play no part in the development of an infective process.

The incidence of rupture of the membranes prior to admission to the hospital was almost 3 times as high in the cases in which puerperal infection occurred than in those with a normal puerperium. Rupture of the membranes occurring more than 12 hours before delivery seemed definitely to predispose to infection. However, premature rupture of the membranes either before the onset of pains or early in labor was apparently of little importance, provided delivery was consummated within the time period mentioned.

Vaginal examination to corroborate or amplify the findings of rectal examination was associated with no added danger.

In the cases in which infection occurred the duration of the first and second stages of labor of both primiparæ and multiparæ was significantly longer than in the cases in which the puerperium was normal. Depending upon parity and the type of delivery, the mean duration varied from 1 to 10½ hours in the two groups, but was persistently higher in the cases of infection.

In the cases of infection, the incidence of perineal tears and of episiotomy was only slightly increased, but the incidence of cervical lacerations of sufficient extent to require immediate repair was 3 times as great as in the cases without infection.

The amount of blood lost subsequent to delivery was significantly greater in the cases with infection than in those in which infection did not occur. The incidence of postpartum hemorrhage (600

c.c. or more) in the two groups was 10.67 and 4.21 per cent., respectively.

In the cases with puerperal infection, intrapartum infection (a temperature during labor of 100.4° F.—38° C.—or above) was almost 4 times as frequent, and intercurrent disease, particularly syphilis, pyelitis, and respiratory infection, was a complicating factor much oftener than in the cases without puerperal infection.

The mean number of days between delivery and the onset of infection as indicated by a rise in the temperature to 100.4° F. (38° C.) or above was three. In 84 per cent. of the cases the onset of infection occurred during the first 4 days. The average duration of the fever was 4.73 days and was longer in patients with operative delivery than in those with spontaneous delivery. In 86 per cent. of the patients the febrile manifestation disappeared within 7 days. The mean highest temperature during the infective process was 102.2° F. (39° C.). The fever reached 103.0° F. (39.4° C.) in fewer than 25 per cent. of the total group.

Cultures of material obtained from the uterus, which were made in more than 60 per cent. of the cases, showed some variety of streptococcus in over 75 per cent., but the streptococcus hemolyticus was found in only 6 per cent. The percentage of anærobic streptococci was higher in cases of spontaneous delivery than in those of operative delivery, whereas the percentage of ærobic non-hemolytic streptococci was higher in the former than in the latter. The colon bacillus was found twice as often after operative as after spontaneous delivery.

Of the total number of women with puerperal infection, 38.4 per cent. were white and 61.6 per cent. were colored. In contrast, 60 per cent. of the infection due to the hemolytic streptococcus occurred in white women, whereas only

one-third and one-fourth of those due to the aerobic nonhemolytic and anaerobic streptococcus, respectively, occurred in white women.

Division of the cases of anaerobic streptococcus infection according to whether delivery was spontaneous or operative approximated closely a similar division of the cases with a normal puerperium, whereas such a division of the cases of infection due to the hemolytic and nonhemolytic varieties of streptococci approached more closely a similar division of the cases with puerperal infection.

The total maternal mortality was 1.28 per cent. The majority of the deaths were due to the hemolytic streptococcus.

In more than one-fourth of the total number of cases of infection the labor and delivery had been normal and without intravaginal manipulation. In all of this large group of cases delivery occurred spontaneously, labor was not prolonged, there were no vaginal examinations, no lacerations occurred in the perineum or cervix, and bleeding after delivery was not excessive. Many of the patients were probably self-infected or infected by digital manipulation during labor, by intercourse shortly before or during the early hours of labor, or through the blood stream from a focus of infection elsewhere in the body. In some, the infection was probably of gonococcal origin. In others it was due undoubtedly to streptococci from the nasal spray of an attendant at the delivery or the patient herself. It cannot be stated definitely that any of these cases were instances of autogenous infection, but the author regards it as significant that, of a large group of cases of puerperal infection, more than 25 per cent. must be classed as unpreventable in the light of present obstetrical knowledge.

**Treatment.**—*Ergotamine Tartrate Poisoning.*—The Council on Pharmacy and Chemistry of the American Medical Association warn against the dangers of overdosage and prolonged use of ergotamine tartrate.

W. M. Yater and J. A. Cahill (J. A. M. A. 106:1625 (May 9) 1936) report the case of a fisherman who had a toxemia with jaundice of unknown etiology. Ergotamine tartrate was injected because of pruritus. Within a week 19 c.c. ( $4\frac{3}{4}$  drams) was used. Gangrene of the feet developed during this time, necessitating amputation of the legs. Study of the vessels showed the changes due to ergotism.

Ergotamine tartrate (gynergen) an efficacious alkaloid of ergot, is capable of producing serious toxic disturbances, usually as a result of overdosage. Chief among these ill effects is gangrene of the extremities.

The cause of the gangrene is occlusion of the medium-sized and small arteries and arterioles by severe constriction and thrombosis. Intimal proliferation of small arteries may also play a rôle. Hyaline degeneration of the vessels follows the vasoconstriction.

The authors caution that the drug probably should not be used in cases of febrile puerperium, in cases of severe toxemia from any cause, or in patients who present evidence of vascular disease, functional or organic.

When the drug is used, careful watch should be kept for the appearance of any toxic symptoms, including signs of impaired peripheral circulation of the hands and feet. On the appearance of these signs, the use of the drug should be discontinued immediately. **Epinephrine** and **papaverine hydrochloride** are suggested for relaxing the *vascular spasm*.

# PEDIATRICS

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## ANEMIA IN CHILDREN

By C. R. RITTERSHOFER, A.B., A.M., M.D.

**HEMATOPOIESIS IN CHILDREN.**—In the fetus, the liver and spleen are active sites of blood formation, especially during the latter part of fetal life. After birth, this function is taken over by the long and flat bones so that hematopoietic tissue fills not only all the flat bones, but also most of the marrow cavity of the long bones. In the infant, the available marrow space in practically all the bones is filled with red marrow tissue and ordinarily no yellow marrow is present. As a consequence of this, a relatively small area is present for expansion and utilization for increased blood cell production as compared with the large yellow marrow spaces in the adult which may readily undergo metaplasia and form hematopoietic tissue in case of need. Anemia, therefore, may result from a lesser drain on the hematopoietic system in a child than would effect the same change in the adult. In children, this smaller intramedullary reserve space forces the individual to turn to extramedullary hematopoiesis relatively early, leading to sudden and marked enlargement of the spleen, liver and lymph glands by hematopoietic metaplasia. When need arises, these centers once more become active and flush the peripheral blood stream with immature, embryonic cell types. (K. D. Blackfan and L. K. Diamond: *Internat. Clin.* 1:112 (Mar.) 1936; R. R. Kracke and H. E. Garver: *Arch.* (530)

*Pediat.* 52:521 (Aug.), 585 (Sept.) 1935.)

In the embryo, red blood cells are formed before the other cellular elements of the blood. These red cells arise from the endothelial cells lining the closed vascular sinusoids of the bone-marrow and develop in the following order: megaloblasts, erythroblasts, normoblasts, reticulocytes and mature erythrocytes. According to R. R. Kracke and H. E. Garver (*loc. cit.*) cell division may occur at any point in this development. Smears of the bone-marrow taken soon after birth show a preponderance of megaloblasts. It is for this reason that any mild stimulation of the bone-marrow of young infants may call forth a variety of immature red cells which might appear to have serious significance without an understanding of the bone-marrow pattern at this age. A similar situation exists for white cells which accounts for the high leukocyte values and the numerous leukoblasts frequently found in the blood of children with ordinary childhood diseases.

**Relation of Fetal Blood to That in Pernicious Anemia During Recovery.**—M. M. Wintrobe and H. B. Shumaker, Jr. (*J. Clin. Investigation* 14:837 (Nov.) 1935), noted in their studies of the size and number of the red cells of the fetus as well as the proportion of erythroblasts and reticulocytes, that in many respects the blood



of the developing fetus resembles that of cases of pernicious anemia which are being subjected to an effective, continuous and extremely potent stimulus to blood formation. They noted also that the red cells of the fetus are larger than those of the adult, and that they vary much more in shape. As the fetus grows, these differences in size begin to disappear and the cells tend to become smaller, changes which are very similar to those in pernicious anemia under liver therapy. On the other hand, a most striking difference is that the bizarre forms of red cells which are so characteristic in pernicious anemia are rarely, if ever, found in the fetal blood. Also, it is unusual to find red cells in fetal blood which are poorly filled with hemoglobin. In fetal blood it was found that numerous nucleated blood cells were a constant feature and that these rapidly diminished in number. The authors felt that the macrocytosis of the newborn really represents a final stage in the development of the blood in the fetus.

It has been shown by Castle and his associates that pernicious anemia develops as the result of the deficiency of an antianemic principle which is formed by the interaction of the extrinsic factor in the diet and an intrinsic factor secreted by the stomach. The administration of this principle, which is found in greatest concentration in liver, is followed by active blood formation, progressively decreasing macrocytosis and a rapid disappearance of anemia. It is the suggestion of the authors that the antianemic principle of Castle may be the same or very similar to the substance which causes the blood of the fetus to develop in the manner described. It is supposed that the fetus obtains its supply of antianemic principle through the placental circulation from the stores of

the mother, since there is presumably no gastric digestion in the fetus.

In *Addisonian anemia*, the degree of anemia is related to the degree of deficiency of antianemic principle. If there is a similar relationship between the quantity of antianemic principle available and the formation of blood in the fetus, the effect of a deficiency of this substance on the mother and the infant may be readily visualized. If the fetus derives antianemic principle from the mother, this may be expected in some instances to cause so great a depletion in the stores of the mother that she develops a macrocytic anemia. It is characteristic of the so-called *pernicious anemia of pregnancy* that it develops only during pregnancy. It is relieved by liver therapy and does not recur following delivery even though liver therapy is discontinued but it may reappear at a succeeding pregnancy. That pernicious anemia of pregnancy is uncommon indicates that the majority of pregnant women during the normal process of digestion form quantities of antianemic principle which are adequate to meet their own requirements and those of the fetus.

An infant for whom an inadequate amount of antianemic principle has been made available during the gestation period may be expected to develop anemia characterized by macrocytosis and by ready response to the administration of liver extract. This should be found to be more common in premature infants, for these have been afforded a shorter period for the acquisition of antianemic principle during the intrauterine period.

**Anemia of Prematurity.**—Premature infants tend to become anemic in the first months of life even if they are not anemic at birth. The normal full term infant always shows a considerable drop in hemoglobin level after

birth, the lowest level being reached at about 2 to 3 months of age. This is followed by a rise in the second 3 months of life, and then, if a sufficiency of iron is not available, a renewed fall. H. M. Mackay (Arch. Dis. Childhood 10:195 (June) 1935) studied a group of prematures in an effort to minimize, if possible, the excessive drop in hemoglobin. It was found that intramuscular injections, transfusion of blood, and iron when given as iron ammonium citrate by mouth, had no prophylactic effect. The hemoglobin values or level during the first 6 months of life of babies weighing at birth from 3 to 5 pounds never dropped below 65 per cent. Mackay suggested that premature and immature babies whose general health and progress have been satisfactory from birth do not usually show any severe anemia during the first 3 months of life.

**ANEMIA OF NEWBORN.**—The chief findings of *primary erythroblastic anemia* of the newborn are a severe hyperchromic anemia, a large number of macrocytes and an increased number of reticulocytes. Suggestive of its hemolytic nature is the increased amount of serum bilirubin formed from the hemoglobin of the destroyed red cells with increased urobilin excretion in the urine and stool. Jaundice is present. The presence of bile thrombi may cause an obstructive jaundice, so that the van den Bergh reaction is then a promptly direct positive or biphasic, and bile is present in the urine. In addition, the blood may show a leukocytosis with a shift to the left, frequently a thrombopenia and an increased bleeding time. The pathology of the conditions shows the persistence of centers of erythropoiesis of the fetal type in various organs. There is a deep yellow staining of the organs and serous membranes, and invariably a hemosiderosis, as shown in the kidneys and reticulo-endothelial system.

P. Cohen (J. Pēdiat. 7:220 (Aug.) 1935) has described another form of anemia of the newborn and contrasts it with the above description of the accepted picture of erythroblastic anemia. In this form the blood picture also shows a hyperchromic, macrocytic anemia, and leukocytosis with a shift to the left, but there the resemblance practically ceases. Erythroblasts are either not present at all or found in the small numbers normal for the newborn. Jaundice is not marked and may even be absent. The blood serum shows an indirect van den Bergh reaction. There is no bile found in the urine and no increase of urobilin. Bleeding time is normal. The reticulocytes are usually either normal in number or but moderately increased, in contrast to the erythroblastic anemia of the newborn. Pathologically, there is no intense bile staining of the organs and serous membranes; no embryonal erythropoietic centers are found in the viscera and hemosiderosis is not encountered. In neither type of anemia was internal hemorrhage present. Cohen emphasizes that a baby born with a skin colored orange because of deep yellow amniotic fluid and golden yellow vernic caseosa is destined to develop anemia. Such a baby should be watched critically every day. When the anemia develops, the child should be promptly, if necessary, transfused repeatedly. The indication for repeated transfusions is repeated drops in the hemoglobin.

**Anemia Due to Infection.**—This form of anemia may simulate every known type of primary anemia. The more frequent methods of development of anemia resulting from infection are: (1) Hemolysis of blood cells due to toxin produced by the infecting organism, such as the hemolytic streptococcus. Thus, a hemolytic type of anemia possibly simulating congenital hemolytic jaundice may be produced. (2) An aplastic

*Similar features*

Erythroblasts  
Color index  
Macrocytosis  
Leukocytosis  
Premature leukocytes  
Placenta  
Vernix caseosa  
Amniotic fluid

*Different features*

Jaundice  
Bile in urine  
Urobilin production  
Bilirubin in serum  
Edema  
Viscera  
Hemosiderosis

*With  
erythroblastosis*

Present  
High, above 1  
Marked  
High  
Present  
Large  
Often deep golden  
Often deep golden  
Marked  
Present  
Excessive  
Very high  
Sometimes present  
Erythropoiesis  
Present

*Without  
erythroblastosis*

Absent  
High, above 1  
Marked  
High  
Present  
Large  
Often golden  
Often golden  
Absent  
Absent  
Normal  
Normal  
Never present  
No erythropoiesis  
Absent

type of anemia in which the red blood cell and hemoglobin levels are lowered simultaneously, due to toxic action on the bone-marrow or other mechanisms of temporary interference with production of blood cells. (3) A secondary purpura with loss of blood from various sites due to lowering of the platelet levels or toxic damage to the capillaries, or a combination of these two factors. (4) An interference with appetite or digestion or the absorption of materials necessary for the formation of red blood cells and hemoglobin, therefore resulting in an anemia of the dietary type.

**Anemia of Scurvy.**—L. G. Parsons and W. C. Smallwood (Arch. Dis. Childhood 10:327 (Aug.) 1935) studied 6 cases by modern hematological methods and were able to demonstrate conclusively both that severe scurvy may occur without any evidence of anemia and that scurvy may be associated with an anemia which is solely the result of a deficient supply of vitamin C. The anemia is a characteristic symptom of scurvy but may not be present in every case. The red cell count may be around 2.5 millions and the hemoglobin around 35 per cent., thus giving a low color index. The anemia may be hypochromic and slightly microcytic. The bleeding

and clotting times and clot retraction were all normal, and there was no diminution in the number of blood platelets. The fact that there is a true anemia of scurvy, the result of a specific deficiency, and that this deficiency is of vitamin C, is shown by the effect of treatment, since all the cases responded rapidly, both hematologically and clinically, to treatment with **orange juice**. A most striking result of treatment with vitamin C was shown by a child, 9 months of age, who had been fed on milk. When orange juice was added a brisk reticulocytosis occurred, reaching its maximum on the eighth day, and on the fifteenth day the red blood cells were normal in number, having been more than doubled, and the hemoglobin had increased from 35 to 70 per cent. The anemia eventually progressed to a complete course. The increase in the nucleated red cells following the onset of treatment was interesting and may be regarded as the result of normoblastic proliferation in the bone-marrow. Both iron and liver preparations free from iron and vitamin C have been proved to be useless in the treatment of scorbutic anemia in adults.

Parsons and Smallwood believe that the anemia of scurvy results from a

general slowing down of the whole process of erythropoiesis which may be so marked as to result in marrow degeneration and aplasia, the resulting anemia being, therefore, normochromic and normocytic; in chronic cases associated with large hemorrhages into the tissues and from mucous membranes, a posthemorrhagic blood picture becomes superimposed and the anemia may then become truly microcytic.

**Nutritional Anemia** (Iron Deficiency Anemia, Hypochromic Microcytic Anemia, Milk Anemia).—K. D. Blackfan and L. K. Diamond (Internat. Clin. 1:112 (Mar.) 1936) divide nutritional anemia or dietary anemia into a number of types dependent upon its causative factor or factors. One type is that due to a specific lack of iron. Another similar type of *iron deficiency anemia* occurs in infants who have been deprived of the opportunity to store iron adequately during intrauterine life because of anemia or inadequate dietary intake in the mother. This inadequate storage by the fetus because of iron deficiency in the mother has no effect on the normally high levels of the blood at birth. But in the neonatal period, when the iron content of the food is low and the infant is dependent upon its stores of iron, the deficiency becomes operative. An iron deficiency anemia results which generally begins to appear after the third month and may last well into the second year if either iron containing food or medicinal iron is not supplied in sufficient quantity. In the case of twins, the anemia occurs after the third month, and may be prevented by supplying the mother with excess amounts of iron or by treating the children with sufficient amounts of medicinal iron.

L. G. Parsons (Brit. M. J. 1:1009 (May 16) 1936) says that the frequency of nutritional anemia may vary in dif-

ferent districts. The reason why all infants do not become anemic in the lactation period is that during the last 3 months of intrauterine life iron and copper are stored in the fetal liver. This store makes up for the lack of these metals in the infant's diet, but by the end of the lactation period it is exhausted; hence, nutritional anemia is certain to develop unless the child is then given a mixed diet containing adequate quantities of iron.

Any interference with the absorption of iron may lead to a dietary anemia. In this group are (1) the anemias dependent upon infection with poor absorption and poor utilization of food substances during the course of the infection and for a variable time thereafter; (2) congenital malformations of the gastrointestinal tract; (3) chronic nutritional disturbances, as celiac disease; (4) intestinal shunts resulting from necessary operative procedures. The treatment of the first is to rid the patient of the infection and to give a **well-balanced diet**, with or without the addition of **iron**. In the second group, additional quantities of **iron** are indicated. In *celiac disease*, the intestinal indigestion should be treated by **dietary measures** with **iron** added. In cases of *intestinal shunts*, **iron** is given by mouth; and in cases of low red blood cell level, **liver** or **liver extract** in combination with **iron** is advocated.

H. K. Faber, C. Mermoud, A. L. Gleason and R. P. Watkins (J. Pediat. 7:435 (Oct.) 1935) studied 10 patients with nutritional anemia and reported that gastric analysis after histamine showed a marked secretory effect. J. W. Ogilvie (Arch. Dis. Childhood 10:143 (June) 1935) studied the *gastric secretions* of 34 children with anemia of various types. Of the 17 patients whose gastric secretion fell within normal limits, the anemia in 9 of them was of

the simple nutritional type; in 3 it was considered to be of the von Jaksch type; in 2 hemolytic; in 1 aplastic; and in 2 it was impossible to relegate the condition into any special category. From the results it did not appear that there is any relationship between the amount of free hydrochloric acid in the gastric secretion and the degree of anemia, nor do any of the types studied show any constant change in the secretion of free acid. It is recognized that the concentration of free hydrochloric acid in the gastric juice has a direct relationship to the capacity for absorbing iron. For this reason, it might be anticipated that diminution or absence of free hydrochloric acid would be found in cases of simple anemia where a low hemoglobin percentage was the prominent feature. Of the 13 cases in which there was defective secretion of hydrochloric acid, 11 had hypochromic anemia. This suggests that deficiency of HCl strongly favors the production of hypochromic anemia but that other causes, *e. g.*, iron starvation, must play a part because 10 out of 18 cases of iron deficiency anemia showed no diminution in HCl secretion.

According to Faber and his associates (*loc. cit.*), the absorption and neutralization of gastric acid by milk (buffer effect particularly by cows' milk) is especially deleterious upon iron absorption from food when, as in infants, the gastric secretion is small in amount and in acid content.

The *blood picture* of nutritional anemia is characterized by hypochromia and microcytosis, the findings in any iron deficiency anemia. As a result of the failure of the body to obtain or to utilize a sufficient supply of iron for its needs there develops a fall in the hemoglobin content of the cells. In the more severe cases there is a low red cell count, but usually the red cell count is normal or slightly elevated.

The red cells show a definite preponderance of microcytes. Poikilocytosis is present in some degree. The average quantity of hemoglobin per cell is invariably reduced much more than the red cell count (low color index, low mean corpuscular hemoglobin).

According to H. K. Faber and his coworkers (*loc. cit.*), a Price-Jones curve shows the majority of the red cells to be less than 4 micra in diameter. After iron therapy is begun, there is a striking response with reticulocytosis and increased size of the red cells accompanying an increase in the hemoglobin. This was followed by a decline of reticulocytes, by an increase of part of the cells to a normal size, some of the cells remaining microcytic in spite of treatment, and by continued rise of the hemoglobin over a period of months. Other significant findings are a reduced hemoglobin concentration in each cell, a figure arrived at by dividing the hemoglobin (Gm. per 100 c.c.) by the number of the red cells in millions. The hematocrit may show a low volume per cent. of the red cells; a microcytosis as shown by the decrease in the cell volume; and a decreased value for the hemoglobin in the cells arrived at by dividing the hemoglobin value in Gm. by the volume per cent.

*Treatment.*—The treatment of nutritional anemia is the administration of iron preferably in a ferrous form. Parsons (*loc. cit.*) says that nutritional anemia of infancy may be prevented by assuring an adequate iron supply both to the mother and to the infant during pregnancy and to the infant during the period of lactation, particularly if the child is artificially fed. The diet of the mother should contain 15 to 20 mg. ( $\frac{1}{4}$  to  $\frac{1}{3}$  grain) of iron a day. It is wise to administer iron to any pregnant woman whose diet is restricted from medical or social reasons. Sugar-

coated tablets of **ferrous sulphate**, 3 grains (0.2 Gm.), may be given 3 times daily.

Blackfan and Diamond (*loc. cit.*) recommend the use of **iron ammonium citrate** to an infant in doses of 1 to 2 Gm. (15 to 30 grains) daily; to the child in 4 to 6 Gm. (1 to 1½ drams) doses daily, preferably dissolved in sweetened orange juice or water as vehicle. It is best to give this between meals for better absorption. **Ferrous sulphate** in doses of 6 to 8 grains (0.4 to 0.5 Gm.) can be given to an infant. In the older child 10 to 12 grains (0.6 to 0.77 Gm.) daily are usually the optimum. When vomiting, diarrhea, or melena occurs, the iron salts should be reduced in amount or stopped for a short time; then begin again with smaller doses and gradually increase the amounts. Such effects are rare, especially with ferrous sulphate. Parsons believes that adequate doses of iron will bring about a cure of the anemia in 4 to 5 weeks. Organic preparations of iron should not be used.

The preparations of inorganic iron which have produced the best results are: ferrous sulphate, 12 grains (0.77 Gm.); reduced iron, 3 grains (0.2 Gm.); and iron and ammonium citrate, 12 grains (0.77 Gm.); in each case divided into 3 doses and given daily. Of these, ferrous sulphate is the most efficacious, although its iron content, while approximately the same as that of iron and ammonium citrate, is very much less than that of an equal amount of reduced iron. Actually 1 grain (0.06 Gm.) of reduced iron contains 54 mg. (⅝ grain) of iron, whereas 1 grain (0.06 Gm.) of ferrous sulphate contains only 12 mg. (⅓ grain).

The reason why ferrous sulphate is more active therapeutically is that all iron has to be converted in the stomach and duodenum into the ferrous form before it is absorbed. Witts has esti-

mated that the percentage of utilization of ferrous sulphate is 14, of reduced iron 0.5 to 2, and of iron and ammonium sulphate in which iron is present in the ferric state 1.5 to 3. It is obvious why 12 grains of ferrous sulphate are so much more efficacious than the same amount of iron and ammonium citrate, and also than 3 grains of reduced iron, although the latter is actually 3 times richer in metallic iron. The disadvantages of ferrous sulphate, that it rapidly oxidizes to the ferric state and that children dislike it, can be overcome by dispensing it with syrup.

Prescriptions for the administration of iron are as follows—to be taken 3 times a day:

℞ *Ferri redact.*..... gr. i (0.06 Gm.)  
*Sacch. alb.*..... gr. iii (0.2 Gm.)  
*Fl. cap.*  
 ℞ *Ferri et ammon. cit.* gr. iv. (0.26 Gm.)  
*Syr. aurant.*..... f3ss (2 c.c.)  
*Aq.* ..... ad. f3ij (8 c.c.)

As for the use of copper, Parsons (*loc. cit.*) says that it may be necessary to give copper before a complete cure is effected. The doses should be 0.5 c.c. (8 minims) of a 1 per cent. solution of **copper sulphate** per kilogram (2½ lbs.) of body weight, best given in milk. Copper probably acts as a catalyst and enables stored or ingested iron to be used in the synthesis of hemoglobin. Very few cases require copper since most of the iron preparations contain copper as an impurity.

Other good iron preparations in use are iron and ammonium citrate 12 per cent. The dose is 0.5 c.c. (8 minims) per Kg. (2½ lbs.) daily. This is equivalent to 10 mg. (⅓ grain) iron per Kg. daily. This should be given preferably with fruit juice. There are many proprietary preparations of iron available, some of them containing ferrous sulphate in capsule form, others containing ferrous sulphate in elixir form.

C. A. Elvehjem, A. Siemers and D. R. Mendenhall (Am. J. Dis. Child. 50:28 (July) 1935) studied healthy infants to whom they gave iron and copper preparations. The majority of the infants received the iron and copper either in the form of a solution or as tablets. The liquid consisted of a solution of powdered **ferric pyrophosphate** and **copper sulphate**. Ferric pyrophosphate was selected because, being readily soluble, odorless and tasteless, and devoid of great astringent properties, it is fairly easily administered. The iron and copper solution was prepared by dissolving 10 Gm. (2½ drams) of ferric pyrophosphate and 0.4 Gm. (4 grains) of copper sulphate in 250 c.c. (½ pint) of distilled water containing 5 per cent. alcohol. One teaspoonful was given daily by incorporating it in the infant's formula or orange juice, or in a glass of milk in the case of older children. In each teaspoonful the child received 25 mg. (⅓ grain) of elemental iron and 1 mg. (⅙ grain) of elemental copper. One tablet was given daily. This treatment caused an increase in the hemoglobin content of the blood from between 9 and 11 grams to from 12 to 13.5 grams per 100 c.c. The addition of smaller amounts of iron and copper did not give as uniform or consistent results as the larger doses. The result suggests that it may be advisable to add small amounts of iron and copper to the diets of some infants to insure an optimum formation of hemoglobin. They did a few studies using 25 mg. (⅓ grain) of iron alone and felt that the response was slower and less extensive than when both iron and copper were used.

G. R. Minot (J. A. M. A. 105:1176 (Oct. 12) 1935) reports that there is little evidence that *deficiency of copper* plays a significant rôle in man in the production of anemia. It may perhaps do so occasionally in infants. In human

anemia the copper in the blood is usually increased. While it is true that in young children, when iron is supplemented by copper, it sometimes enhances the rate of hemoglobin formation, in adults, copper therapy is very seldom of value. It is not difficult to create serious copper poisoning by administering relatively small amounts of copper.

**Sickle Cell Anemia.**—Two follow-ups on children with sickle cell anemia who had their **spleens removed** were reported by J. F. Landon and H. A. Patterson (J. Pediat. 7:472 (Oct.) 1935). The children were 4 and 5 years of age and were checked after 5 and 7 years respectively. Both children have continued to show moderate variable anemia. However, the immediate improvement in the blood picture was remarkable in each case. One case has remained clinically well with freedom from abdominal or joint pains. The other has continued to be moderately anemic with exacerbations always accompanying the respiratory infections to which she is susceptible.

**Splenectomy in Anemia.**—M. Wollstein and K. V. Kreidel (Am. J. Dis. Child. 51:765 (Apr.) 1936) have reported the effects of splenectomy on the blood picture in cases of traumatic rupture of the spleen, rheumatic disease, splenomegaly of undetermined origin, congenital hemolytic icterus, and Cooley's anemia.

In the case of *traumatic rupture of the spleen*, the platelets were increased, as a rule, reaching their peak about 5 to 10 days after operation. None of the 3 children reported showed postoperative anemia. On the contrary the hemoglobin content and the number of red cells rose steadily during the time of hospitalization, and the high levels were maintained for 7 months in 1 case and for 6 weeks in another.

In 20 cases of *rheumatic fever* who had their spleens removed there was no anemia either before or after the operation. The platelets reached their peak from the sixth to the fourteenth day afterward.

Three cases of *congenital hemolytic jaundice* showed a postoperative rise of platelets, in 1 case reaching more than 1,000,000, a level which was maintained for several months. Three cases showed an initial drop in the reticulocyte count to less than 1 per cent. on the second or third day, this level being maintained throughout the periods of observation, 2½, 10 and 18 months, respectively. Three patients whose condition was typical showed a steady increase in hemoglobin and red cells and were no longer anemic on dismissal.

In patients with *Cooley's anemia*, the response of the platelets was most irregular in onset, number and duration of the increase, nor was it ever as high or of as long duration as in the other groups. The patients became more and more anemic and did not show lympho-

cytosis. Nucleated red cells in the peripheral blood increased in number throughout the period of postoperative life.

**Hydrocephalus Associated With Anemia.**—B. B. Bhatia (Brit. M. J. 1:60 (Jan. 11) 1936) reports a case of a child who had been normal until 1 year of age, when he began to develop signs of hydrocephalus, papilledema with atrophy of the nasal halves of the discs, loss of vision, a patent anterior fontanel, localized convulsions and loss of consciousness. Blood examination disclosed a severe anemia showing 900,000 red blood cells and 10 per cent. hemoglobin. Treatment with **cows' milk, fruit juice, fresh liver**, and an iron and **copper** mixture resulted in rapid improvement of the anemia and a disappearance of the hydrocephalic symptoms. The convulsions ceased in 2 months' time and the vision gradually returned. The author suggests that a highly hydremic condition of the blood might easily lead to an increased production of cerebrospinal fluid and hydrocephalus.

## CHICKENPOX

By ROBERT A. LYON, A.B., A.M., M.D.

**Complications.**—In recent years, central nervous system complications of chickenpox have been observed with increasing frequency. A thorough review of this subject has been made recently by E. A. Underwood (Brit. J. Dis. Child. 32:83 (Apr.-June), 177 (July-Sept.) 1935). In the literature were found reports of 119 cases in which lesions of the central nervous system followed varicella and these could be classified into groups of (1) meningo-encephalitis; (2) true encephalitis; (3) myelitis; (4) neuritis and polyneuritis; (5) ocular manifestations; and (6) other conditions. In addition, there was a

small group of patients in whom nervous symptoms occurred as prodromal symptoms of the chickenpox. True encephalitis was the most common type of complication and was noted in about half of the group. Of this group cerebellar forms were frequent and the author reported an instance which had been observed in a girl 8 years of age who had developed the symptoms of cerebellar encephalitis 5 days after the onset of chickenpox. The fact that the cerebellum is most frequently involved differentiates the encephalitis which followed chickenpox from that of the several other infections.



In the records of 107 patients, the results of the encephalitis were recorded and of this group 12 died and 16 had serious sequelæ. The first symptoms of the complications developed between 3 and 20 days after the eruption of the chickenpox, but they occurred most frequently on the fourth to the tenth day.

The reports in the literature varied in frequency from year to year but were most numerous during the years 1925 to 1932, the largest number occurring in 1929. The complications were noted in all parts of Europe and the United States but the incidence seemed to be greatest in France and Italy.

## DIABETES MELLITUS IN CHILDREN

By WALDO E. NELSON, A.B., M.D.

**Treatment.** — **INSULIN.** — The most important contribution of the past year is unquestionably the introduction of **protamine insulin** by Hagedorn (H. C. Hagedorn, B. N. Jensen, N. B. Krarup and I. Wodstrup, J. A. M. A. 106:177 (Jan. 18) 1936). This development of a precipitated insulin compound which is slowly soluble in tissue fluid makes it possible to maintain the blood sugar of the diabetic child at a more even level and even in some instances to approximate that of the normal child. Recently, an improvement has been effected which permits protamine insulin to be marketed already mixed. This compound, to which 0.08 mg. of zinc is added to each 5 c.c. vial, will remain potent for 6 months if kept in a cold place.

The clinical use of protamine insulin is still in the trial period and it is quite possible that not only a more suitable compound but more efficient methods for its use will be devised. At present there are in general 2 methods. The first is the so-called "evening administration," as recommended by Hagedorn and by H. F. Root, P. White, A. Marble and E. Stotz (*Ibid.* 106:180 (Jan. 19) 1936). Regular insulin is given at breakfast time and again at noon, if necessary, and protamine is used for the evening injection. This method is particularly beneficial when the morning blood sugar

is high and a midnight dose would otherwise be required. Protamine insulin may be given in the morning, as suggested by R. G. Sprague, B. B. Blum, A. E. Osterberg, E. J. Kepler and R. M. Wilder (*Ibid.* 106:1701 (May 16) 1936). This method, with or without regular insulin at the same time but in a different location, has considerable merit. It has been shown that if a sufficiently large dose of protamine insulin is given it will exert a hypoglycemic effect for 24 hours or longer. The REVIEWER'S experience has been, however, that if a dose is given sufficient to maintain the blood sugar of the following morning at a satisfactory level, then the blood sugar at noon and at the end of the afternoon on the day of administration are quite high. Further increases in the dosage of protamine insulin result in hypoglycemic reactions early the following morning without materially improving the blood sugar level of the preceding day. Entirely satisfactory results are being secured by the combined method of giving a dose of each (protamine insulin and regular insulin) shortly before breakfast. With this régime the majority of the children have been maintained in satisfactory glyceemic equilibrium. Protamine insulin cannot, however, supplant regular insulin at the present time. There is still need for the more rapidly acting insulin to supplement

the protamine insulin, particularly in the treatment of coma and precoma, as well as during infections, and preceding and following surgical procedures, when regular insulin is the one of choice.

Since the introduction of protamine insulin, a **crystalline insulin** has been made available for clinical trial. The action of this insulin seems to be midway between that of regular and protamine insulin, in that it exerts a more rapid but less prolonged response than that of protamine and a slightly less rapid but more prolonged response than regular insulin. Satisfactory clinical experience with the use of crystalline insulin is reported by H. A. Freund and S. Adler (*Ibid.* 107:573 (Aug. 22) 1936) and by S. S. Altshuler and R. Leiser (*Ibid.* 107:1626 (Nov. 14) 1936). The REVIEWER's experience with this insulin has been more limited than with protamine; however, so far he has not been able to secure as satisfactory glycemic equilibrium with 2 doses of crystalline insulin (A. M. and P. M.) as with the combined morning dose of protamine and regular insulin.

DIET. — There are no new developments in the dietary treatment. The tendency to a more liberal carbohydrate intake continues but with definite limitations in most instances. Most clinicians seem to feel that the advantages obtained in relation to insulin adjustment, control of weight, adequacy of diet, as well as the disciplining effect upon the child of reasonable restriction, justify such a plan. However, reports of the use of more or less "free diets" continue to appear, as for example those of C. W. Herlitz (*Acta. paediat.* (Supp. 2, Art. 2) 18:1, 1935) and of B. Söderling (*Ibid.* (Supp. 2, Art. 1) 18:1, 1935). Herlitz limited the carbohydrate to a certain extent, whereas Söderling apparently imposed no restrictions whatsoever. Both report that the children developed satis-

factorily, that coma and hypoglycemic reactions were infrequent and that the need for insulin was not materially increased and even in some instances was actually decreased.

The statement of Söderling to the effect that this form of treatment should be especially suitable for the unintelligent patient or for those who live at a distance from the clinic is open to question. It would seem that children falling in either of these categories are in even greater need of definite instruction as well as restriction. It is the REVIEWER's opinion that the maintenance of diabetic children upon "free diets" is still within the experimental field and should be so considered.

M. G. Vorhaus, R. R. Williams, and R. E. Waterman (*Am. J. Digest. Dis. and Nutrition* 2:541 (Nov.) 1935) have studied the effect of administration of **crystalline vitamin B<sub>1</sub>** upon the blood sugar of diabetics. Experimental deficiency of vitamin B<sub>1</sub> causes a disturbance of the carbohydrate metabolism characterized by a rise in the blood sugar and in the glycogen content of liver and muscle. Although a diminished carbohydrate tolerance is encountered in other forms of avitaminosis and aberrations from the normal state, it is most consistent and marked in experimental B<sub>1</sub> deficiency. The authors point out that the clinical syndrome of diabetes mellitus is suggestive of a nutritional disturbance and that there is reason to believe that a deficiency of vitamin B<sub>1</sub> may be a factor in the production and clinical course of this condition.

In a series of 11 cases of proved diabetes mellitus to whom an average of 10 mg. ( $\frac{1}{6}$  grain) of vitamin B<sub>1</sub> was administered daily for 28 consecutive days, 6 showed an increased carbohydrate utilization and 5 cases showed no increase. Two of the 6 positive cases lost the gain in carbohydrate utilization

as soon as the administration of vitamin B<sub>1</sub> was stopped. In 4 cases the increase continued for a period ranging from 2 to 10 months and 2 of these 4 are still maintaining the gain. In the discussion of this paper, J. E. Thomas called attention to the fact that diabetics who had a restricted carbohydrate diet are apt to have a small cereal intake and possibly a vitamin B deficiency. Thus, a deficiency of vitamin B would almost certainly aggravate the symptoms of diabetes. It might even cause a latent diabetes to become active. If that were the case, administration of vitamin B would, unquestionably, alleviate the condition to some extent, though it would not cure the diabetes. Such an observation would not establish a causative relationship between vitamin B deficiency and diabetes. The most logical conclusion to be drawn from these studies is that vitamin B deficiency is apt to be an accompaniment of diabetes, and in the treatment of diabetes, such a condition should be looked for and, if present, treated appropriately.

The relationship between vitamin B and normal carbohydrate metabolism appears to be a fairly well established fact; whether that is the primary function of the vitamin metabolism is another question, but there does not seem to be any doubt that deficiency of vitamin B<sub>1</sub> results in an excess of blood sugar and an excess of liver glycogen. In diabetes, while there is an increase in blood sugar, there is a deficiency of liver glycogen.

**Complications.**—An instance of diabetes mellitus with evidence of *dry gangrene* of the foot in an infant 11 days of age is reported by M. A. Limper and A. J. Miller (Am. J. Dis. Child. 50: 1216 (Nov.) 1935). The infant died when it was 3 weeks of age. Clinically there was dry gangrene involving the left lower extremity to the mid-portion of the thigh. Necropsy revealed that this

was caused by thrombosis which involved the aorta and extended into all its branches from the level of the left renal artery downward. Examination of the pancreas showed pancreatitis involving the head of the pancreas and acute degeneration of the islands of Langerhans. The mother of this infant had mumps at the time of delivery and the possibility of the pancreatitis being due to the virus of mumps is suggested.

An instance of diabetes mellitus in a child 11 years of age who also had *hypothyroidism* is reported by H. M. Greenwald and W. S. Collens (*Ibid.* 50: 979 (Oct.) 1935). There have been numerous reports of hyperglycemia and glycosuria associated with hyperthyroidism as well as improvement in sugar tolerance after thyroidectomy. Hyperglycemia in cases of hyperthyroidism is presumably due to an increased glycogenolytic function of the liver which results in a depletion of the glycogen stores. In hypothyroidism the blood sugar may be normal or low and there is often an increased tolerance for sugar. This is probably due to an increased ability to fill the glycogen depots owing to the lack of the normal antagonistic effect of the thyroid. When the basal metabolic rate is raised by thyroid ingestion, the tolerance of sugar is lowered. In the case cited, the administration of more than 2 grains (0.13 Gm.) of desiccated thyroid a day sufficiently decreased the child's tolerance to necessitate an increase in the dose of insulin. When 2 grains (0.13 Gm.) of desiccated thyroid a day were administered, the urine was sugar-free with from 20 to 25 units of insulin per day on a diet containing 150 grams of carbohydrates, 55 grams of protein and 55 grams of fat; whereas if 2½ or 3 grains (0.16 or 0.2 Gm.) of desiccated thyroid were given, sugar appeared in the urine.

**NONDIABETIC GLYCOSURIA.**

—The separation of diabetic glycosuria from nondiabetic glycosuria is of unquestioned diagnostic importance. The classification of nondiabetic or benign glycosuria is at least of academic interest. A. E. Fischer (Am. J. Dis. Child. 50:166 (July) 1935) suggests that so-called *renal diabetes* or *renal glycosuria* may be characterized by an intermittent as well as continuous glycosuria, and reports 3 instances of benign renal glycosuria which illustrate this point. One of these children had a continuous glycosuria and spilled sugar into the urine at a blood level as low as 60 mg. per cent. The other two had somewhat higher renal thresholds for sugar, which passed into the urine only at 135 mg. per cent. and 155 mg. per cent., respectively. Fischer contends that continuous renal glycosuria is only a descriptive term. The question whether the glycosuria is continuous or intermittent is dependent solely on the threshold level of the particular patient. The diagnostic criteria for renal glycosuria are the benign nature of the glycosuria, normal blood sugar curve, and a normal respiratory quotient. It is suggested that a high blood sugar curve, indicating a temporary loss of tolerance, can occur even in renal glycosuria. Further, acetonuria may occur in association with renal glycosuria if a large amount of sugar is excreted and an insufficient amount is left in the body for complete oxidation of fatty acids. The *prognosis* of continuous or low threshold renal glycosuria is excellent. Diabetes mellitus has not developed in such patients who have been observed for years. The cases with a higher threshold also have a good prognosis. There is some evidence to suggest that renal glycosuria may be an inherited quality. No treatment of renal glycosuria is necessary. The author suggests that frequent meals of a some-

what higher caloric intake than normal may be given in order to replace the food and energy lost by glycosuria and by the incomplete oxidation of fat.

An instance of prolonged *galactosuria* associated with disturbance of nutrition and development is reported by H. H. Mason and M. E. Turner (*Ibid.* 50:359 Aug.) 1935). The infant did not gain normally as long as the diet contained milk. There was an enlargement of the liver, slight enlargement of the spleen and superficial lymph nodes, a positive van den Bergh reaction, secondary anemia, osteoporosis of the bones, and albumin and sugar in the urine. The sugar in the urine was shown to be galactose. Removal of milk from the diet resulted in the disappearance of the sugar and albumin from the urine, decrease in the size of the liver and spleen, disappearance of the positive van den Bergh reaction, improvement in the blood cellular elements, and in the appearance of the bones, as well as a rapid gain in weight. The blood sugar curves after the injection of dextrose and levulose were within normal limits, but after the injection of lactose and galactose the curves were abnormal. When the diet contained no milk, the blood sugar curve throughout the entire day was within normal limits. When each meal contained 200 c.c. of milk and 10 grams of added lactose, the curve for the blood sugar was abnormal in that the fluctuations were narrow and were due almost entirely to changes in the level of blood galactose. The level of blood dextrose remained low throughout the day.

Mason and Turner suggest that the primary difficulty in this case was a lesion or functional disturbance of the liver that lowered the ability of this organ to convert galactose into glycogen without seriously impairing the other functions of the liver, and that the de-

rangement of the other tissues was the result of relative starvation due to the continuously low level of blood dextrose.

**HYPOGLYCEMIA IN NEW-BORN INFANT OF A DIABETIC MOTHER.**—An instance of spontaneous hypoglycemia occurring immediately after birth in an infant of a diabetic mother is reported by L. M. Randall and E. H. Ryneerson (Proc. Staff. Meet., Mayo Clin. 10:705 (Nov. 6) 1935). Blood taken from the umbilical cord contained 194 mg. of sugar per 100 c.c. of blood; that of the mother 280 mg. per 100 c.c. Two hours later, the infant's blood sugar was 43 mg. per

100 c.c. (micro method). At this time the infant had convulsive movements of its head. The blood sugar was elevated by means of oral and subcutaneous administration of glucose. The authors suggested the possibility that the infant, having been part of a diabetic mother for so long a time, required a higher level of blood sugar than the infant of a normal mother. It is highly important that the carbohydrate metabolism of such an infant should be carefully followed to determine in which direction the glucose tolerance will go and what relation such a state has to the later development of diabetes.

## ENDOCRINE DISTURBANCES IN CHILDREN

By JOSEF WARKANY, M.D.

**PITUITARY.**—*Simmonds' Disease.*—E. Kylin (Ergebn. d. inn. Med. u. Kinderh. 49:1, 1935) has reviewed the literature and reported 12 cases of Simmonds' disease. He believes it to be a clinical syndrome, caused by destruction of the hypophysis as well as by a pathologic process in the hypothalamic region and the stalk of the hypophysis. The subjective *symptoms* are exhaustion; disturbance of sleep, psychic disturbances, such as depression, apathy and diminished intelligence and memory; lack of appetite; "stomach trouble"; vertigo; headache; and decreased libido; while cachexia, loss of weight, atrophy and a yellowish-brown discoloration of the skin, dry brittle nails, carious teeth, constipation, low blood-pressure, low blood sugar and decreased metabolic rate are the objective signs. The syndrome is difficult to differentiate from Addison's disease and pluriglandular insufficiency. The *treatment* consists of the administration of **anterior lobe** tablets, injection of extracts of the anterior lobe or the **transplantation** of

an **hypophysis** of an animal to the patient. The correct diagnosis and treatment render the prognosis more favorable.

A case diagnosed as Simmonds' disease has been reported by R. C. Moehlig (Endocrinology 20:155 (Mar.) 1936). The patient, a 15-year-old girl, suffered from loss of weight and strength, decaying teeth, falling hair, irregular menstruation, mental lethargy, dryness of the skin and anorexia. She was treated with antuitrin-S, extract of the suprarenal cortex (eschatin), insulin alone and with glucose, pituitary tablets, cod-liver oil, sunshine, a high caloric diet and forced feeding. In spite of these measures, she died 17 months after the appearance of the initial symptoms.

**Laurence-Biedl Syndrome.**—The cases of 3 brothers with polydactylism and varying degrees of hereditary cerebral defects have been described by M. Molitch, R. G. Gladen and A. W. Pigott (Endocrinology 19:682 (Nov.-Dec.) 1935). One brother had retinitis pigmentosa; one had myopia and a tessell-

lated appearance of the retina; and the third, a mild visual defect with strabismus. The authors believe that all cases, occurring in the same family, having all or nearly all of the cardinal symptoms of the Laurence-Moon-Biedl syndrome (mental deficiency, obesity, retinitis pigmentosa, hypogenitalism and polydactylism), should be listed as such; while nonfamilial cases not having all the cardinal symptoms should not be included.

*Obesity combined with atypical chondrodystrophy* has been observed by H. Grenet and P. Isaac-Georges (Arch. de méd. d. enf. 38:725 (Dec.) 1935). Most of the symptoms resembled those of Morquio's disease. Mental development was normal and other members of the family were not affected.

*Pituitary Dwarfism.*—Eleven cases of pituitary dwarfism were treated with anterior pituitary extracts by R. L. Schaefer (Endocrinology 20:64 (Jan.) 1936). An increase in growth was induced by this treatment. Thyroid medication was recommended as an adjunct. The author emphasized the fact that in these patients all measurements are proportionate but below the minimal normal. Delay in osseous development was said to be a good prognostic sign. G. B. Dorff (*Ibid.* 19:209 (Mar.-Apr.) 1935) has also reported a case of infantilism in a 16 year old boy. The symptoms were stunted growth, sexual infantilism and a delay in the closure of certain epiphyses. For a number of years the patient had not increased in size. After treatment with *antuitrin-S* (1 c.c. 3 times a week, with a total of 43 injections) the patient gained 1 inch in height, and on *phyone* ( $\frac{1}{2}$  to 1 c.c. 3 times a week with a total of about 30 c.c.) he gained another  $2\frac{1}{4}$  inches, or a total of  $3\frac{1}{4}$  inches in 18 months.

Diabetes mellitus, sexual infantilism and varying degrees of dwarfism were

observed in 8 patients, 16 to 20 years of age, by R. B. Gibson and W. M. Fowler (Arch. Int. Med. 57:695 (Apr.) 1936). The sella turcica was normal or even smaller than normal in each case. These authors believe that the dwarfism is not the result of the diabetic condition.

An influence of insulin on the sex glands or the pituitary must be assumed, however, in order to explain the phenomenon described by G. A. Williams and R. L. Williams (J. A. M. A. 104:1208 (Apr. 6) 1935). Administration of 5 to 10 units of insulin daily to a poorly developed, nondiabetic girl,  $8\frac{1}{2}$  years of age, resulted in acceleration of bodily growth and sexual development. Discontinuance of the insulin was followed by regression of the secondary sexual characteristics, but body growth continued at a less rapid rate. Another course of treatments with insulin after a lapse of 10 months resulted in the reappearance of the sexual phenomena. However, these disappeared again as soon as the insulin was omitted.

Cases of 2 siblings having prenatal malformations of the pars intermedia and posterior lobe of the pituitary have been reported by B. Chown (Brit. J. Surg. 23:552 (Jan.) 1936). Deformities simulating severe rickets were present at birth. The children failed to grow adequately and became dwarfs. Nervous symptoms such as convulsions, crying spells, etc., were manifested. There were hypercalcemia, calcium casts in the urine, calcium deposits in the renal lymphatics, focal necrosis in the kidneys and a pyelonephritis. On the basis of these extremely interesting cases, Chown developed a theory of *renal rickets*, differing widely from the usual view. Instead of considering the renal changes as the primary disease, and the stunted growth and bone changes as secondary effects due to abnormal

metabolic conditions, he believes that the pituitary gland is primarily at fault and causes, by way of the parathyroid and thyroid glands, dwarfism, polyuria, infantilism and dilatation of the urinary tract (diencephalon), as well as abnormal bone development and metaphysal absorption without the formation of new bone. The minerals thus made available are excreted by the kidney and renal calcinosis develops. Chown believes the nephritis to be secondary to an abnormal mineral metabolism and not to be the cause of it.

**THYROID.**—In a review of the problem of *goiter* in childhood, E. Wieland (Arch. f. Kinderh. 105:129, 1935) concludes that goiter, which is merely a clinical symptom, is chiefly a problem of growth. The first stage is a hyperplasia, leading to a secretion that quantitatively and qualitatively contains sufficient iodine. The character of goiter, both morphologically and functionally, differs under different geographical conditions and according to the age of the child. *Diffuse goiter* is found more frequently in children, being parenchymatous and epithelial in the new born, and *follicular* in children of school age or at puberty. These forms respond favorably to treatment with **iodine** without developing toxic symptoms. *Nodular goiter*, which is rare in childhood, is found in certain goiter belts and in cretinism. *Exophthalmic goiter* is exceptional in childhood.

Since the various forms of goiter differ morphologically and functionally, different *etiologic factors* must be considered. The water as a "carrier" of the hypothetical injurious factor, chronic intestinal infections, radioactive emanations, improper nutrition, and lack of iodine must be taken into account. A universal, systematic *prophylaxis* with **iodized salt** is the only way to prevent goiter in children. There are no toxic

effects if the salt contains not more than 0.5 Gm. ( $7\frac{1}{2}$  grains) of potassium iodide to 100 Kg. ( $45\frac{1}{2}$  lbs.) of salt (50 gamma per day per person), and if the treatment is restricted to the first 2 or 3 decades of life—including pregnant and nursing women and excluding persons who show a lability of the vegetative nervous system.

G. B. Dorff (J. Pediat. 6:788 (June) 1935) has reported cases of *masked hypothyroidism* in children with mental or physical retardation. The symptoms were similar to those of sporadic cretinism. Retarded osseous development was an important factor in diagnosis. In children under 8 years of age the basal metabolic rate was usually not significant. **Thyroid therapy** was efficacious in cases with delay in osseous development, a low basal metabolic rate, and a lack of response to other forms of treatment.

It is well known that hyperthyroidism and glycosuria often occur together. The association of *hypothyroidism and diabetes mellitus*, however, is considered to be rare. H. M. Greenwald and W. S. Collens (Am. J. Dis. Child. 50:979 (Oct.) 1935) have reported the case of a girl, aged  $7\frac{1}{2}$  years with polyuria and polydipsia. Sugar, acetone and diacetic acid were found in the urine. The blood sugar was 220 mg. per cent. At the same time, the broad saddle nose, thick lips, protuberant abdomen, hoarse voice, delayed development of the centers of ossification and a basal metabolic rate of  $-29$  justified the diagnosis of hypothyroidism. In fact, this diagnosis was made by a physician when the child was 4 months old and desiccated thyroid ( $\frac{1}{4}$  grain—0.016 Gm.—twice daily) was given from that time until she was seen by Greenwald and Collens when 7 years of age. This treatment was then discontinued and **dietary treatment and insulin** were commenced. Response to the treatment was good. The blood sugar

was reduced to 70 mg. per cent. and the urine became sugar free. After **thyroid** medication was resumed, the child required a higher dose of insulin, and any attempt to increase the dose of desiccated thyroid above 2 grains (0.13 Gm.) per day resulted in the appearance of sugar in the urine.

In a study of *root resorption* in patients requiring orthodontic treatment, H. Becks (Internat. J. Orthodontia 22:445 (May) 1936) has found that systemic diseases occur with great frequency. He believes that the root resorptions are not produced by mechanical force alone. Among the endocrine disturbances, *hypothyroidism* seems to occupy a dominant place. It was found in 60 per cent. of the treated and in 40 per cent. of the untreated cases of root resorption. Hypothyroidism combined with other endocrine disturbances was found in 80 per cent. of the group with and in 60 per cent. of the group without previous orthodontic treatment. Five patients with *acromegaly* were found to suffer from root resorption, although only 1 had been treated orthodontically.

Three cases of a *syndrome* characterized by familial occurrence in males, *i. e.*, a facies resembling hypothyroidism; optic neuritis; normal mentality; limited extension of the joints; thick, pudgy extremities; thick bones; retarded epiphyseal osteogenesis; thick, dry, coarse hair and skin areas; enlarged abdomen; hepatosplenomegaly and tendency toward lymphocytic leukopenia were described by W. A. Reilly (Endocrinology 19:639 (Nov.-Dec.) 1935). At necropsy, degeneration and necrosis in the anterior lobe of the pituitary were found in 1 case. There was mild hyperplasia of the thyroid combined with an increase of interlobular connective tissue and degeneration in many of the alveolar cells. The thymus was enlarged.

P. C. Elliott (J. Pediat. 6:204 (Feb.) 1935) describes a case of severe *exophthalmic goiter* in a child, aged 2½ years, whose symptoms began when she was 6 months old. "The benefits of an iodine remission were lost in order to employ x-ray therapy instead of surgery. When this failed to halt the progress of the condition, bilateral superior pole ligation was performed and later hemi-total thyroidectomy. Mild hypothyroidism resulted."

E. Rose, E. K. Rose and E. P. Pendergrass (*Ibid.* 7:325 (Sept.) 1935) recommend adequate **irradiation** in the treatment of *hyperthyroidism* in children and younger adolescents. If improvement does not occur within 3 months, radiation should be stopped and preparation for **thyroidectomy** begun.

It has been pointed out by K. Wallis (Monatschr. f. Kinderh. 61:161, 1935) that the incidence of *hyperthyroidism* in children seems to be much smaller in Europe than in North America. The author reports 2 cases, one of which, in a 7-year-old girl, showed clinical as well as improvement of the basal metabolic rate, carbohydrate metabolism and leukocyte findings after treatment with **diiodotyrosine**.

*Carcinoma of the thyroid gland* of the malignant, rapidly metastasizing, papilliferous type, has been reported by A. B. Taylor and B. M. Wilkinson (Arch. Dis. Childhood 10:99 (Apr.) 1935). The patient died 4 months after the first symptoms appeared. R. L. J. Kennedy (J. Pediat. 7:631 (Nov.) 1935) has also reported cases of carcinoma of the thyroid gland in children under 14 years of age. On the basis of cases treated operatively at the Mayo Clinic, approximately 1 per cent. of carcinomas of the thyroid gland affected children, and they were slightly more than one-twentieth as frequent as was exophthalmic goiter. Of Kennedy's 8 cases,



7 of the patients were girls and 1 a boy. It is evident that enlargement of the cervical lymph nodes may appear before any involvement of the thyroid gland itself. Later *symptoms* are hoarseness, dyspnea and a sensation of pressure. Metastasis may involve the regional lymph nodes and the lungs. *Diagnosis* is usually established by microscopic examination of the primary tumor or the regional lymph nodes. Due to the low grade malignancy and the high grade radiosensitiveness, the *prognosis* is usually favorable. In early cases that are *encapsulated*, **removal of the growth** is sufficient; if *not encapsulated* the **entire lobe should be removed**. If there are *metastatic* lesions, the **neighboring nodes should be removed** as well. All patients should be treated **postoperatively with radium**.

**Basal Metabolism.**—The basal metabolic rates of 87 normal girls between the ages of 10 and 20 years with exceptional economic advantages have been studied by F. B. Talbot, E. B. Wilson and J. Worcester (*Ibid.* 7:655 (Nov.) 1935). These authors state that the percentage deviation in normal girls may be more than plus or minus 12 per cent. above or below the standards given in one-third of these cases, and that too much emphasis should not be laid on minor variations outside the commonly used plus or minus 10 per cent. limit. Variations of between minus 12 and minus 20 per cent. were studied, those at the lower limit being considered as significant, while those of less than 17 per cent. probably are not. Variations of more than plus or minus 20 per cent. were considered to be probably significant.

**THYMUS GLAND.**—A study of variations of weights in all parts of the thymus and in the number of Hassall corpuscles has been made by E. Boyd (*Am. J. Dis. Child.* 51:313 (Feb.) 1936). At the age of puberty, the

medulla and Hassall corpuscles begin the process of involution, while involution of the lymphoid tissue begins at the age of 4 years. Connective tissue and fat continue to increase until old age. In persons dying of disease, fortuitous involution has progressed within 1 to 7 days far enough to reduce the weight of the parenchyma and connective tissue, but without affecting Hassall corpuscles. In persons with an illness lasting 1 week or more, all parts including the Hassall corpuscles are decreased, while in exophthalmic goiter the parenchymatous structures are increased in weight or number.

A boy, aged 13 years, having *osteopsathyrosis* was treated for 3 months with injections of 1 c.c. of Hanson's **thymus extract** by E. W. Secord, R. M. Wilder and M. S. Henderson (*Proc. Staff Meet., Mayo Clin.* 11:1 (Jan. 2) 1936). A total of 90 c.c. was administered. Eight months after the treatment was discontinued, the boy appeared to be improved. On x-ray examination a marked improvement in the density and strength of the femurs was noted. The cortex of the bone was thicker than before. No significant changes were noted in the spine or ribs.

**PINEAL BODY.**—G. Horrax (*Arch. Neurol. and Psychiat.* 35:215 (Feb.) 1936) has reported 2 cases of *pineal tumor*. One in a boy, aged 10 years, was demonstrated by ventriculography. It was accompanied by macrogenitosomia precox. After **decompression** and **x-ray** therapy, the boy had a period of normal activity for a year and became more normally child-like in appearance.

**SUPRARENAL GLANDS.**—Forty-three cases of *suprarenal hemorrhage* were observed at necropsy by C. E. Snelling and I. H. Erb (*J. Pediat.* 6:22 (Jan.) 1935). The symptoms observed in the 15 newborn infants were

either collapse or hyperirritability, such as convulsions, twitching or screaming. In the older age group, 15 cases were observed after septicemia, meningitis or chronic renal disease. In 4 patients the causative agent was burns; in one it was caused by a severe accident; while in another case it was due to transfusion from an incompatible donor. In 6 cases in which death was caused by intercurrent disease, calcification was found and in 1 case fibrosis.

C. E. Snelling and I. H. Erb (*Ibid.* 7:669 (Nov.) 1935) have reported a case of *suprarenal atrophy* in a boy, aged 9½ years, with microcardia. There was a marked craving for salt. Temporary improvement was attained with the intravenous injection of **saline solution** and **adrenalin therapy**. Marked asthenia, emaciation and weakness preceded pigmentation of the skin. The blood sugar curve was prolonged and was somewhat diabetic in type. The electrocardiogram revealed a low potential. The child died after convulsions, which may have been a manifestation of hypoglycemia. The cause of the atrophy was unexplained.

In a case of *hereditary ectodermal dysplasia*, S. J. Thannhauser (*J. A. M. A.* 106:908 (Mar. 14) 1936) found symptoms suggesting insufficiency of the adrenal medulla. A low fasting blood sugar, a flat sugar tolerance curve, scattered pigmentation of the skin and low blood-pressure were present. The author suggests the possibility that the adrenal medulla, which is of ectodermal origin, may be involved in the hereditary ectodermal dysplasia.

Seventeen cases of *neuroblastoma* or *sympathoblastoma of the adrenal* in children have been reviewed by J. A. Askin and C. F. Geschickter (*J. Pediat.* 7:157 (Aug.) 1935). These tumors are seen usually in patients under 3 years of age, although in this series 7 of the children

had passed that age. Males predominated over females in the ratio of 11 to 5. Trauma was recorded as an etiologic factor in 5 instances. In 15 cases there was an abdominal mass which was usually not painful. Vomiting and fever occurred in some cases. Loss of weight was frequent, but emaciation and exophthalmos were late symptoms. Joint pain was infrequent. There was an overlapping of the Pepper (metastases chiefly in the liver) and the Hutchinson (metastases in the bones) syndromes.

In a discussion of the *differential diagnosis* Askin and Geschickter stated that: Wilms' tumor (embryoma of the kidney) is more frequent in children after 2 years of age, is accompanied by hematuria or urinary obstruction and responds fairly well to deep x-ray therapy. Retroperitoneal lymphosarcoma is more common in adults and responds rapidly to irradiation. Leukemia, rheumatic fever and appendicitis are difficult to rule out until the tumor mass becomes palpable. If involvement of the bones is found, the following diseases must be considered. The Schüller-Christian syndrome is found in older patients and the lesions respond to x-ray therapy. The same is true of chloroma, in which there is a more definite periosteal reaction as well as general signs of leukemia. Ewing's sarcoma is rarely found before the age of 4 years. It is most common in the long bones, where it produces splitting of the subperiosteal and cortical layers in the so-called onion peel fashion. The *prognosis* in neuroblastoma is unfavorable; the course is rapid, and death usually takes place within a few months. Another case of the same condition was reported by F. Eckhardt (*Monatsher. f. Kinderh.* 61:127, 1934) in a 5½ year old boy. The onset was slow and without characteristic signs. There were increasing cachexia and anemia without the typical changes

of the differential blood picture, as well as enlargement of the veins of the skull, hemorrhagic tumor of the skull with corresponding defects on x-ray examination, and tachycardia. A biopsy of one of the tumors of the skull revealed the nature of the process. Eckhardt believes that the clinical picture differs in the child and the adult. In the latter, the symptoms are paroxysmal hypertension, sudden attacks of pallor, dryness of the skin, tremor, vertigo and palpitation of the heart, which are interpreted as symptoms of adrenalin poisoning. On the other hand, in the child, the picture is that of a malignant growth with formation of metastases but without symptoms of adrenalin poisoning.

A *paraganglioma* in each adrenal gland was found at autopsy in a girl, aged 14 years, by D. N. Kremer (Arch. Int. Med. 57:999 (May) 1936). The patient had hypertension and died of cerebral thrombosis. The condition was diagnosed clinically as hypertensive heart disease with associated glomerular nephritis. Early symptoms, such as precordial pain, cardiac palpitation and dysynea, were suggestive of hypertensive crises, although in 2 readings the blood-pressure was normal.

**TESTICLES.**—The influence of **antuitrin-S** on aspermia, testicular atrophy and undescended testicles has been described by W. L. Brosius (Endocrinology 19:69 (Jan.-Feb.) 1935). In 3 out of 5 cases of *aspermia*, favorable effects were obtained after injection of 1 to 2 c.c. of **P. U.** (found in the urine of women during pregnancy) 2 to 4 times weekly for periods of from 5 to 21 weeks. Motile spermatozoa were demonstrated after treatment in 2 out of 5 subjects with nonmotile spermatozoa. In 9 cases of *undescended testicles* **P. U.** was given in doses varying from 1 to 3 c.c., from 1 to 3 times weekly. There was complete descent in 6 cases, and in

2 cases partial descent was attained. Some of these patients were also given **thyroid** medication. B. Webster (J. A. M. A. 104:2157 (June 15) 1935) obtained favorable results in 10 out of 11 cases of undescended testicles during the period of treatment.

Only in those cases of undescended testis in which the pituitary gland is sexually underactive does the water-soluble fraction of pregnancy urine seem to have a favorable effect, according to H. S. Rubinstein (Endocrinology 20:192 (Mar.) 1936). It then leads to a stimulation of the interstitial cells of the testicle and results in descent where mechanical obstruction does not exist.

The view that the interstitial cells of the testes are important in the development of the secondary sex characteristics of the male has again been emphasized by C. A. Stewart, E. T. Bell and A. B. Roehlke (Am. J. Cancer 26:144 (Jan.) 1936), who report a case of *interstitial cell tumor of the testes* in a boy aged 5 years. The growth led to appearance of pubic hair, enlargement of the penis, and development of the testes containing the tumor almost to the point of formation of spermatozoa.

An interesting accidental effect was observed by H. Koplin (J. A. M. A. 106:374 (Feb. 1) 1936) after administration of 1 c.c. of **antuitrin-S**, 3 times a week, in a 30-months-old boy with *undescended testes*. After treatment for 3 weeks, the scrotum began to turn pink and became swollen. In the left groin a small tumor the size of a normal testicle appeared. After 8 weeks of treatment the child began to have enuresis and developed polydipsia. There was a large trace of sugar in the urine and a specific gravity of 1028. Three weeks after the **antuitrin-S** was stopped, the urine became sugar-free and the polydipsia and enuresis disappeared.

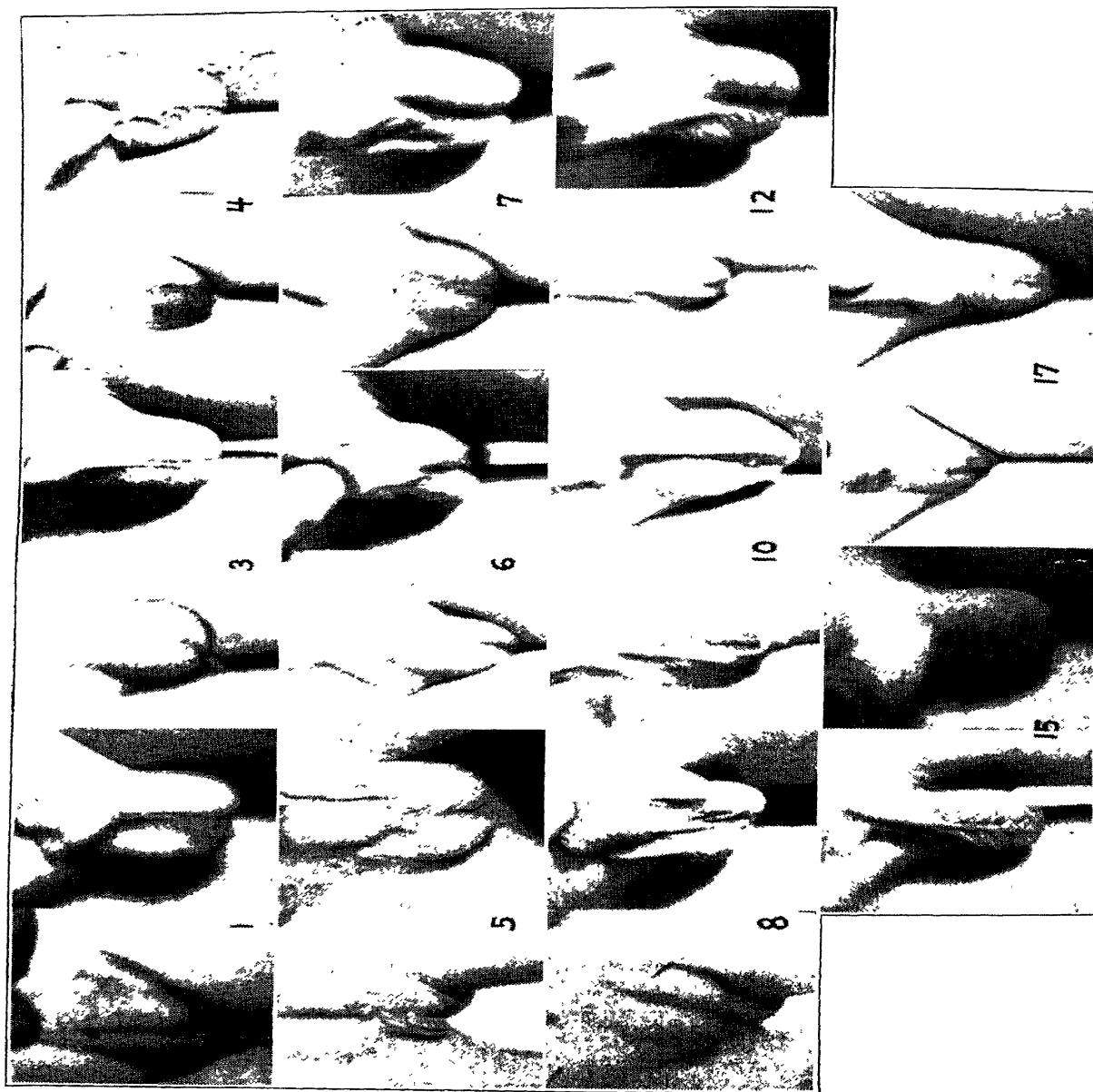


Fig. 1.—Appearance before and after injections of gonadotropic extract of pituitary in 11 cases of cryptorchidism. (Werner, Kelling, Ellersieck and Johns: J. A. M. A.)

Twenty-five injections of 1 c.c. of **antuitrin-S** (5 within 60 days) led to interesting results in a boy, aged 11 years, with mental retardation, obesity, diabetes insipidus and *cryptorchidism*, according to A. A. Allen and J. S. Stokes (J. A. M. A. 106:780 (Mar. 7) 1936). After 15 injections, both testes were palpable in the scrotum and all symptoms of polyuria and polydipsia had disappeared. After 25 injections, the child's mentality had developed remarkably, his weight was reduced by about 7 pounds, and the diabetes was apparently cured. When the boy was reëxamined 9 months later, no signs of retrogression had appeared.

Success in the treatment of undescended testes with **gonadotropic extract of the pituitary** is also reported by A. A. Werner, D. Kelling, D. Ellersieck and G. A. Johns (J. A. M. A. 106:1541 (May 2) 1936). In a group of 17 cryptorchid boys, ranging in age from 5 to 13 years, descent of the testes was observed in 12 after treatment with this extract. One to 2 c.c. of an extract con-

taining 10 rat units of gonadotropic principle per c.c. was injected either every day or every other day. In 9 of the 12 boys, descent of the testes occurred within 15 days. Examples of the authors' results are illustrated in Fig. 1. They conclude that to correct cryptorchidism, anterior pituitary gonadotropic extract should be administered for at least 30 days before resorting to operative procedures.

**OVARY.**—An experimental study of possible damage to the ovaries after administration of ovarian follicular hormone has been conducted by E. Allen and A. W. Diddle (Am. J. Obst. and Gynec. 29:83 (Jan.) 1935). This hormone is used in the treatment of *gonorrheal vaginitis* in children. Over periods of 28 and 39 days, 1265 to 1390 rat units of **amniotin** were injected into immature monkeys. In a careful study of the ovaries no damage could be detected. The authors conclude that comparable doses of this hormone may be prescribed for children without harmful effects upon the ovaries.

## DISEASES OF THE DIGESTIVE SYSTEM IN CHILDREN

By WALDO E. NELSON, A.B., M.D.

### DIAPHRAGMATIC HERNIA.—

An instance of congenital shortening of the esophagus in a 12 year old girl is reported by J. B. Gillespie (J. Pediat. 8:38 (Jan.) 1936). There were no symptoms referable to this condition. Figure 1 shows that a portion of the stomach lies within the thoracic cavity. The author very wisely points out that if this condition is to be considered as a diaphragmatic hernia or hernia of the stomach through the diaphragm, the term "congenitally fixed" or "congenitally irreducible" should qualify the term "hernia." It is important to differentiate shortening of the esophagus with

the resulting partial or complete intrathoracic stomach from simple herniation of the stomach into the thoracic cavity, since the latter condition in many instances is amenable to surgical treatment, whereas a markedly short esophagus makes successful surgical repair extremely unlikely.

### APPENDICITIS.—Symptoms.—

In distinguishing between visceral and somatic symptoms of appendicitis in children, S. Nixon and B. Nixon (Am. J. Dis. Child. 51:1296 (June) 1936) stress the importance of making the diagnosis during the stage of early visceral symptoms since the course of the disease is

so rapid after the onset of somatic symptoms. There is absence of muscular rigidity and local tenderness during the stage of endo-appendicitis. The tension on the nerve endings in the wall of the appendix may be insufficient to produce characteristic visceral pain but may be responsible for restlessness, sleeplessness, anorexia or a temporary abnormal in-

crease in temperature is most unusual in this stage and the child does not appear particularly ill. The abdomen is usually "silent" and is neither distended nor retracted. Contrary to the general opinion, there is an absence of muscular rigidity and tenderness either in the central area where the pain is manifested or in the right iliac triangle. This is



Fig. 1.—The short esophagus enters the uppermost cardiac portion of stomach. Approximately one-half of stomach lies within the thoracic cavity. (J. B. Gillespie: J. Pediat.)

crease in appetite, with a departure from normal intestinal habits. Some mechanical interference, such as hyperplasia of the abundant lymphoid tissue in the appendix or exudation caused by the acute inflammatory changes may obstruct the proximal lumen. These vague symptoms may then change as the peristalsis becomes more exaggerated and the threshold of visceral pain is overcome. This results in colicky pain in the upper part of the abdomen, which is at first moderate but rapidly increases in severity and is manifested, among other ways, by paroxysms of crying. An in-

crease in temperature is most unusual in this stage and the child does not appear particularly ill. The abdomen is usually "silent" and is neither distended nor retracted. Contrary to the general opinion, there is an absence of muscular rigidity and tenderness either in the central area where the pain is manifested or in the right iliac triangle. This is followed by pain in the right iliac fossa, muscular rigidity and tenderness and, usually, a gradual rise in temperature. This second phase of appendicitis represents involvement of the cerebrospinal nervous system from irritation of the parietal peritoneum by the underlying diseased viscus. The severity is in direct proportion to the degree of peritoneal involvement.

The Nixons warn that in any case of acute abdominal disease, the possibility of appendicitis should not be excluded because of the absence of the typical sequence of symptoms, since this may be

distorted by any of the following factors: evacuation of the irritating appendiceal contents into the cecum; patency of the lumen throughout the entire attack; interference with the neuromuscular mechanism of the viscus; interposition of some abdominal structure which protects the spinal nerves of the parietal peritoneum, and ptosis of the appendix into the pelvis. This theory of the separation of visceral and somatic symptoms is based upon the assumption that irritation of the splanchnic nerves of the viscus and of the somatic nerves of the parietal peritoneum are involved independently in the production of pain, of tenderness and of rigidity. The authors believe that an acceptance of the hypothesis of an independent involvement of the sympathetic and the cerebrospinal nervous system at different stages of the disease will assist in eradicating diagnostic confusion in many cases and will be conducive to early appendectomy, with a resulting lowered mortality rate.

**Differential Diagnosis.**—In a recent epidemic of approximately 300 cases of Sonne-Duval and atypical Flexner *bacillary dysentery*, J. Felsen (*Ibid.* 50:661 (Sept.) 1935) reports a form of bacillary dysentery in which the symptoms were somewhat similar to those of acute appendicitis in about 3 per cent. of the cases. Most of these cases occurred in children. The usual clinical features of the appendicular type of bacillary dysentery are: colicky abdominal pain, often localized in the right lower quadrant; vomiting and only moderate pyrexia, with a temperature of from 101° to 102° F. (38.3° to 38.8° C.). Lassitude, anorexia and headache may occur in the prodromal period, but these symptoms are less likely to occur in the Sonne-Duval than in the Flexner type of dysentery. Tenderness is usually present at or about McBurney's point; it may be most evident on rebound and

may shift with change in the position of the body. The ileum and colon are generally spastic and this is considered an important diagnostic feature, since intestinal spasm occurs early in the disease and persists for some time. A history of diarrhea is helpful in making a diagnosis, particularly if mucus and bright red blood have been present. However, in some of the Felsen's patients no diarrhea occurred, and in almost one-half of the cases obstinate constipation followed subsidence of acute symptoms after from the sixth to the tenth day. This is important, since appendicular symptoms may occur in cases of bacillary dysentery on or after the sixth day, when diarrhea is no longer a prominent feature. The following table of differential diagnosis is reproduced from this article:

#### DIFFERENTIAL DIAGNOSIS

| <i>Appendicular Form of Bacillary Dysentery.</i>                           | <i>Acute Suppurative Appendicitis.</i>                                  |
|--|---|
| 1. History of "food poisoning."  | 1. Sudden onset, often without history of dietary indiscretion.         |
| 2. History of diarrhea or contact with a person who has had diarrhea.      | 2. Diarrhea unusual; no history of contact.                             |
| 3. Moderate initial pyrexia.   | 3. Higher initial pyrexia.  |
| 4. Lax abdominal wall.   | 4. Muscular rigidity.   |
| 5. Spastic ileum or sigmoid flexure.                                       | 5. No spasm of ileum or sigmoid flexure.                                |
| 6. Enlarged mesenteric nodes felt at the ileocecal angle in thin children. | 6. Mesenteric nodes usually not felt.                                   |
| 7. Patient appearing well and relatively comfortable.                      | 7. Patient acutely ill.   |
| 8. Absence of leukocytosis; leukopenia frequent.                           | 8. Leukocytosis with increase in band forms.                            |
| 9. Positive culture obtained from the feces early in the disease.          | 9. Culture obtained from the feces negative for <i>B. dysenteriae</i> . |

## DIFFERENTIAL DIAGNOSIS—Continued

| <i>Appendicular Form of Bacillary Dysentery.</i>  | <i>Acute Suppurative Appendicitis.</i>  |
|---|---|
| 10. Agglutination titer present late in the disease.  | 10. No agglutination of <i>B. dysenteriae</i> except in some patients who have recently recovered from the disease. |
| 11. Diagnostic bacteriophage present.   | 11. No diagnostic bacteriophage except as noted in circumstances specified in item 10.                              |
| 12. Appendix grossly appearing normal.  | 12. Appendix acutely inflamed.  |
| 13. Mesenteric adenitis.  | 13. Mesenteric adenitis rarely as pronounced as in bacillary dysentery.   |
| 14. Appendicular lymphoid hyperplasia with focal necroses of the solitary lymph nodules.                                | 14. Appendicular necrosis with supuration or gangrene.  |
| 15. Inflammation of the distal portion of the ileum in some cases.  | 15. No inflammation of the distal portion of the ileum.   |
| 16. Hyperplasia of Peyer's patches and solitary acuminated lymph nodules in the appendix, ileum and colon.              | 16. Ileum and colon not involved; intramural acute suppurative inflammation of all the coats of the appendix.       |
| 17. Appendicular symptoms usually clear until* within 24 hours or less, but persisting diarrhea of increasing severity. | 17. Appendicular symptoms persisting.   |
| 18. Removal of appendix unnecessary.  | 18. Removal of appendix imperative.   |

An instance of appendicitis in an infant 6 months of age, in which one of the findings was the passage of stools containing small amounts of fresh blood thoroughly mixed with the fecal matter, is reported by R. M. Greenthal (Arch. Pediat. 52:639 (Sep.) 1935). Mention is made of this case since in the differential diagnosis of the conditions

causing blood in the stools, acute appendicitis should be considered as well as such other conditions as *gastroenteritis*, *Meckel's diverticulum*, *intussusception* and *intestinal polyyps*.

Another instance of acute appendicitis resembling *intussusception* is reported by F. H. Coleman (Lancet 1:1008 (May 2) 1936). In this infant there was a sudden onset 9 hours before the examination. There were attacks of pain associated with drawing up of the legs and screaming. At the onset the mother had noticed the passage of bright blood and mucus in the stool. No tumor could be detected on rectal examination. At operation an inflamed appendix was discovered. There was no evidence of intussusception.

**CELIAC DISEASE.—Pathogenesis and Treatment.**—A new concept of the pathogenesis of celiac disease together with recommendations for treatment are suggested by A. E. Wade (J. Pediat. 8:563 (May) 1936). In 2 instances a marked improvement in symptoms was observed by the simple expedient of administering a stimulant to gastrointestinal peristalsis. The rationale for this treatment followed a chance observation of improvement after administration of a laxative. In contrast to the expected result, the stools became formed and the nocturia of the following night disappeared and the night weight loss was not appreciable. In view of this experience, daily morning doses of *cas-cara sagrada* were prescribed. Following this, it was noted that there was a normal intestinal peristalsis, approximately two-thirds of the urine output was voided during the day and one-third during the night; the former 2 to 3 pound night weight loss was reduced from  $\frac{1}{2}$  to  $1\frac{1}{4}$  pounds; there was a normal response of the blood sugar curve in contrast to the flat one prior to treatment; the child had a better appetite and sense of well-

\* Probably clear up or disappear (REVIEWER).



being; the stools became formed, and over a period of 6 months there was no recurrence of the celiac type of stools. This plan of treatment was repeated in another child whose weight had been stationary for a period of 4 years. After 5 months of treatment on a moderately high protein but otherwise balanced diet, together with 5 minims (0.3 c.c.) of posterior pituitary extract twice daily, or at other times 10 minims (0.6 c.c.) of fluid extract of *cascara sagrada* given once daily, there was a weight gain of 10 pounds and a gain in height of  $\frac{1}{2}$  inch.

In both children there seemed to be an extreme atony of the urinary bladder. Wade suggests the possibility that the cause of celiac disease may be concerned with a smooth muscle dystrophy, or a disturbance of innervation of the sympathetic nervous system. In view of the evidence that fats are apparently digested but poorly absorbed, the carbohydrates are digested and are slowly absorbed, and the proteins are digested and absorbed, it is suggested that the symptoms of the disease are the result of disturbed intestinal absorption. This disturbed absorption may be the result of decreased intestinal motility and distension. It may be that suspension of the ordinary muscular contraction results in a lowered circulation of the lacteal and blood vessels of the intestinal wall, and that their selective absorption is largely suspended. Whether or not there is sufficient ground to substantiate such a hypothesis, the results of treatment of these 2 children are sufficiently striking to warrant further clinical trial along the lines indicated.

**Prognosis.**—In an extensive review of their experience with celiac disease, A. V. Neale, W. C. Smallwood and F. Shippam (*Am. J. Dis. Child.* 50:1502 (Dec.) 1935) point out that the prog-

nosis may be quite favorable if the condition is treated early and adequately. Celiac disease develops during the early years of childhood, at any time after the age of 6 months. The greatest mortality rate is found in children about 2 years of age. In addition to the long-continued dietetic treatment, it is emphasized that **vitamin D** or **ultraviolet irradiation** is important in the cure of rickets, tetany and osteoporosis. The ability to absorb fat normally from the bowel and clinical and biochemical cure usually result after from 2 to 6 years of strict dietetic treatment. However, clinical recovery may precede by 1 or 2 years the disappearance of all excess fat from the stool as determined by biochemical assay. The cessation of steatorrhea is characterized by marked improvement in nutrition and rapid growth of bone, particularly is this true at the time of puberty. Thus it is pointed out that the end-result in regard to general nutrition, development and stature is particularly satisfactory. In the cases recorded in which adequate treatment had been maintained, there was little or no dwarfing at the time of adolescence. Sexual development was not inhibited and even in the cases of more severe disease, menstruation began within the usual age period. The danger of neglect of treatment is demonstrated in the case of a child who at the age of 18 years, still had steatorrhea, active rickets and growth deformities of the bones. Hematologic studies were carried out in 16 of the recorded cases. A microcytic, hypochromic anemia was found commonly in those cases with steatorrhea. In some instances this anemia persisted after the cessation of the steatorrhea, even when a full varied diet was given. The response to iron therapy was slow in some instances and it was found that relapses in the anemia may follow cessa-

tion of this treatment. Fig. 2 illustrates the excellent development in one of the authors' cases.

**STEATORRHEA.**—*Differential Diagnosis.*—A. H. Parmelee (Am. J. Dis. Child. 50: 1418 (Dec.) 1935) calls attention to a type of steatorrhea which may be distinguished from celiac disease as it is ordinarily described. The term

presented this clinical picture during life have shown at necropsy a constant pathologic process which is distinguished by marked fibrosis and great diminution in the amount of secretory gland tissue in the pancreas, and by pulmonary changes characterized by purulent bronchitis and bronchiolitis and, at times, numerous widely disseminated miliary abscesses

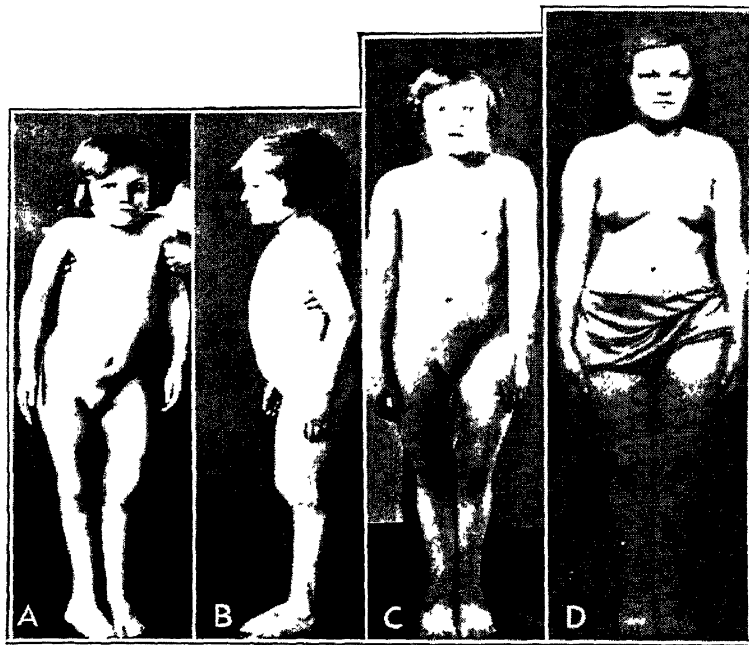


Fig. 2.—Series of photographs of D. B.: *A* and *B* were taken in 1928; *C*, in 1930; and *D*, in 1933 at age of 18. (Neale, Smallwood and Shippam: Am. J. Dis. Childhood.)

“congenital steatorrhea” is used to describe this clinical condition which is said to differ from the usual picture of celiac disease in the following respects: (1) The onset is in the first week of life regardless of the type of feeding. (2) The stools contain an excessive amount of neutral fat as compared to the amount of fatty acid and of soaps. (3) Free fat in the form of an oily substance often is passed with the feces in large amounts when such food as butter, cream or cod-liver oil is fed. (4) The patient never overcomes this digestive abnormality. According to Parmelee, patients who have

and changes in the alveolar walls indicative of chronic irritation.

In the discussion of this paper D. C. Darrow, quoting Thaysen, suggests that the important question in the examination of the stools is probably not how much neutral fat is present or whether the fats are split into fatty acids and soap, but whether there is evidence of deficiency in the absorption of nitrogens. In other words, patients with true pancreatic insufficiencies with diminution in the amount of secretory gland tissues will have a deficiency in the absorption of nitrogen.

## DIPHTHERIA

By ROBERT A. LYON, A.B., A.M., M.D.

In the annual survey of the *mortality* from diphtheria in 93 cities of the United States for the year 1935, (J. A. M. A. 106:2060 (June 13) 1936), it was reported that 19 of the cities had had no deaths from diphtheria. Cities in the New England states and the middle Atlantic states had excellent records for the past year, but there was some increase in the incidence of diphtheria in the cities of the south Atlantic states and the cities of the east north central states, including Ohio, Indiana, Illinois, Michigan, and Wisconsin, and there was also a slight increase among the cities of the mountain and Pacific states. Other portions of the country showed some improvement over the figures of last year. It seems apparent that in localities where diphtheria immunization is carried on extensively diphtheria mortality rates were reduced.

**Bacteriology.**—Further studies of the incidence of *gravis*, *mitis* and *intermediate* type of diphtheria bacilli in Manchester, England, have been made in a series of 940 patients by D. T. Robinson and F. N. Marshall (Lancet 2:441 (Aug. 24) 1935). They found that the incidence of the *gravis* type of bacillus had increased considerably over that of the previous year, the number of intermediate types had decreased and the incidence of *mitis* types was approximately the same in the 2 years. As in the previous study, severe clinical diphtheria was found to accompany infections of the *gravis* type and mild infections usually occurred with the *mitis* type. Laryngeal diphtheria was frequently caused by the *mitis* type of organism. The diphtheria infections produced by the *gravis* type of bacillus were usually more resistant to injections of antiserum and occurred more frequently in Schick-negative patients than did the *mitis* types of infec-

tion. There were 13 patients who developed clinical diphtheria in spite of the fact that their Schick reactions had been negative at the onset of the illness. The majority of these patients had mild or only moderately severe infections, but 2 died. In these 2 cases the diphtheritic membrane covered only a small area of the pharynx and large doses of antitoxin did not prevent the spread of the membrane or the severe course of the disease. Another group of 11 patients who had received the immunizing treatment but had had no subsequent Schick tests likewise contracted the illness and of this group 1 patient died and 2 others developed paralysis. All were infected with *gravis* or intermediate types of the bacillus. Robinson and Marshall raised the question whether or not the antitoxin level which produces a negative Schick test is sufficient to protect patients against infection with more malignant types of diphtheria bacillus. It was their recommendation that patients who were frequently exposed or who were living in communities in which *gravis* types of infection were common should be given additional prophylactic injections of the immunizing material even though their Schick reactions were negative.

In a bacteriologic examination of 166 patients with diphtheria, J. F. Murray (J. Path. and Bact. 41:97 (July) 1935) found that it was possible to group the bacteria into the 3 general classifications of *gravis*, *mitis* and *intermediate types*, according to their appearance and fermentation reactions. Morphologically, the intermediate types were almost always slender forms but heavily barred and segmented with occasional clubbing of the ends. The *gravis* types were usually short and solid with metachromatic granules located in the poles, and the *mitis* types varied considerably in their

shapes but were generally long slender organisms containing many metachromatic granules. In respect to their association with the clinical types of diphtheria, the intermediate types were usually isolated from severe diphtheritic infections, while the gravis types were recovered from milder clinical infections, as a rule, but the number of patients with gravis infections was relatively small. Mitis types generally were associated with mild infections. In a subsequent study of 250 strains of the diphtheria bacillus, J. F. Murray (*Ibid.* 41: 439 (Nov.) 1935) found that these 3 types of diphtheria bacilli differed serologically from each other, and that each of these groups contained subgroups with characteristic differences in regard to the absorption of agglutinins.

Other types of diphtheria bacilli besides these 3 groups were also found by H. A. Wright and M. H. Christison (*Ibid.*) 41:447 (Nov.) 1935). In a study of 613 strains of the bacillus they were able to isolate the 3 types of *mitis*, *intermediate* and *gravis* and also 3 *additional types*, which varied in their cultural aspects and in their reactions in animals. It was thought that the incidence of the different types of diphtheria bacilli varied considerably in different communities. In Edinburgh it was found that 24.5 per cent. of the strains of diphtheria bacilli did not belong to the original 3 strains described previously. Therefore, they devised a new classification consisting in 6 general groups which would be more suitable for use in communities where greater variation of the bacilli occurred. In the city of Edinburgh it was found difficult to correlate the severity of the illness with the different types of diphtheria bacilli which were isolated from these patients, except that, as a rule, type I seemed to be associated with milder cases. Because of their failure to obtain distinct correla-

tions of the clinical course of the disease with the types of the diphtheria bacilli isolated, Wright and Christison wondered whether other factors such as the social, economic, immunological and epidemiological conditions in certain areas might vary considerably and be partly responsible for the differences in severity of illness and types of organisms isolated.

The spontaneous variation of diphtheria microorganisms from bacilli to coccoid forms and the reverse has been observed by G. L. Hobby (*J. Infect. Dis.* 57:186 (Sept.-Oct.) 1935). The diphtherial coccus was found to be able to produce toxin as well as the forms of diphtheria bacillus. Certain cultures of the coccoid forms were found to be susceptible to bacteriophage isolated from the intestinal contents of patients with diphtheria, from the intestinal contents and peritoneal washings of guinea pigs which had been infected with diphtheria, and from raw cultures which had stood at room temperatures from 4 to 6 weeks. Some types of the bacteriophage were active against the coccoid form but not against other forms of the microorganism, while certain strains of the rod forms were increased in virulence by the bacteriophage.

**Clinical Types.**—*Diphtheritic meningitis* was observed in a boy 2½ years of age by F. G. Carlson and H. W. Morgan (*J. A. M. A.* 106:1164 (Apr. 4) 1936). The diphtheria bacilli apparently gained entrance to the meninges by way of a diphtheritic otitis media and mastoiditis. Cultures of the throat were likewise positive for the Klebs-Löffler bacilli, but there was no clinical evidence of the disease in that location. The organisms recovered from the cerebrospinal fluid grew in pure culture and the virulence tests were positive. The child died 9 days after admission to the hospital.

**Immunization.**—The immunization of large numbers of school children in Toronto has been followed by a great reduction in the incidence and mortality of the disease, according to the report of N. E. McKinnon and M. A. Ross (*Ibid.* 105:1325 (Oct. 26) 1935). During the period of 1927 to 1930, more than 16,000 school children received 3 doses of toxoid, and in the years 1929-30, 29,000 additional children were treated. Previous to this immunization work the incidence of diphtheria in the city of Toronto had been relatively stable and the expected rate was 222 a year, but following the immunization campaign only 23 cases of the disease occurred, a reduction of 90 per cent. In the year 1934, only 18 cases of diphtheria were reported and for a period of 15 months there was not a single death from that disease. It was thought that the immunization not only protected the individuals who received the treatment, but reduced the chances of the infection being carried to susceptible individuals.

Immunization against diphtheria has been conducted on a large scale in Hungary during the last few years and the results have been reported by F. Faragó (*Am. J. Hyg.* 22:495 (Nov.) 1935). Preliminary Schick tests performed on children of ages ranging from 1 to 12 years showed considerable variations in the percentage of positive reactions, depending on the district in which the children lived. The number of positives varied from 25 per cent. in the older age groups in certain localities to 95 per cent. in the younger children in other regions. The 4297 Schick positive children were given an injection of 1 c.c. of **alum precipitated toxoid**. Of about 2400 who could be followed over a period of 1 year, negative Schick reactions were obtained in 93.7 per cent. *Reactions* consisting of cold abscess for-

mation occurred in 0.3 to 0.01 per cent. and in none of these patients were the results severe. It was felt that the reactions could be reduced in number by injecting the materials deep in the subcutaneous tissue.

The advantage of a single injection of **alum precipitated toxoid** for the immunization of large groups of children or of children widely scattered in rural districts has been recognized by J. E. Haine (*Brit. M. J.* 2:896 (Nov. 9) 1935). A group of 1160 children, between the ages of 5 and 14 years, in rural communities, were treated with 1 injection. Two or 3 months after the administration of the alum toxoid, 837 of the children were tested by the Schick method and more than 91 per cent. were found to be negative. There were no systemic reactions and local inflammation was mild in the younger children but rather severe in children 12 to 14 years of age. A small group of 17 adults had marked local reactions and 2 of this group of patients developed severe systemic symptoms. Although Haine was aware of the importance of subsequent Schick testing, he realized that the time and difficulty of performing this test in large groups of children, especially of rural districts, was difficult and since there was some question in regard to the reliability of the negative Schick reactions in guaranteeing immunity to diphtheria, he believed that it was not always practical to perform this test. It was Haine's practice, however, to make the tests on certain groups of children from time to time to be sure that the method of immunization and the material employed was effective.

Similar results have been obtained with the 1 injection method of **alum precipitated toxoid** in the immunization of children by M. Naughten, J. H. White and A. Foley (*Ibid.* 2:898 (Nov. 9) 1935). A group of 130 susceptible

children of an average age of about 11 years who were residing in institutions were given a single injection of the alum toxoid. About 93 per cent. of the group became Schick-negative 2 months after the injections. The *reactions* in the great majority of instances were mild. In 1 case there was a small sterile abscess which developed at the site of the injection, and in 6 other children a brawny indurated area occurred in the entire arm, accompanied by local heat and a generalized arthritis. Considering the fact that the average age of this group of children was 11 years, it was thought that the reactions were relatively mild.

Two *doses* of alum toxoid seem to be more effective than the single injection methods in producing immunity to diphtheria. G. Chesney (*Ibid.* 1:208 (Feb. 1) 1936) employed 0.1 or 0.2 c.c. of alum toxoid as an initial dose and 0.4 c.c. as the second dose 3 to 4 weeks later, in a group of 184 children 1 to 14 years of age. Negative Schick reactions were obtained in 99.3 per cent. of the group after 6 weeks or more. H. J. Parish (*Ibid.* 1:209 (Feb. 1) 1936) used doses of 0.1 c.c. and 0.2 to 0.5 c.c. at intervals of 3 weeks and obtained negative Schick reactions in 100 per cent. of a group of children. Such small divided doses seemed to be more effective than single injections of larger amounts of alum toxoid, and the very small initial dose served as an indication of the sensitivity of the patient to the material.

The *reactions* to immunizing agents which have been observed in school children in the Los Angeles schools during the past 11 years have been reported by L. Kositz (J. Pediat. 7:662 (Nov.) 1935). After employing various types of immunizing agents, it was found that the 2 injections of ordinary toxoid produced the highest number of negative Schick reactions. Alum precipitated toxoid was

likewise an effective antigen and produced the most rapid immunity but was less satisfactory for general use, especially in older children, because of the large number of severe reactions it produced. Of a group of 1360 children treated with the *alum precipitated toxoid*, 17 developed abscesses with drainage at the site of the injection; in another group of 653 children, 2 developed local abscesses; and in a third group of 123 children immunized by this method 6 developed abscesses which required incision. These reactions were much more frequently observed in children over 5 years of age.

*Reactions* to the injection of *alum toxoid* have been reported by A. L. Shafton (*Ibid.* 8:676 (June) 1936). A group of 101 children who had received 1 c.c. of alum precipitated toxoid subcutaneously were observed closely for 24 hours. Forty-eight children had elevations of temperature within 24 hours after the injection, 22 developed frank abscesses, and 3 more had indurated areas followed by scar formation. All of these reactions occurred in children who were 8 years of age or older. In spite of the formation of abscesses, which either required incision or were allowed to open spontaneously, 99 per cent. of the patients developed immunity after a period of 5 months. Eighty-six of the entire group had received toxin-antitoxin at least 4 months to 10 years previously and the records of the other children were not available.

The value of the *Moloney test* for the detection of individuals who might react unfavorably to injections of diphtheria toxoid or alum toxoid has been reviewed by E. A. Underwood (J. Hyg. 35:449 (Dec.) 1935). This test consists of the intradermal injection of 0.2 c.c. of a solution of diphtheria toxoid diluted 1:200 with normal saline solution. A positive reaction develops in 24 hours

and reaches its height in 48 hours. The reactions may be classified according to their size and severity. Underwood considered an area of redness more than 40 mm. in diameter with induration as a "definite reaction" (+ + +); a smaller area of redness 10 to 40 mm. in diameter with slight induration as a "mild reaction" (+ +); and lesser degrees of redness, not due to the trauma of injection, as a "*faint reaction*" (+).

Moloney tests were performed on 2666 children and young adults and 596 tests were made on individuals who had recently been given the immunizing toxoid treatment. In the summary of the results it was stated that sensitivity to toxoid was detected in a few instances in very young infants but 2 plus and 3 plus reactions did not occur in more than 3 per cent. of any groups of children under 5 years of age. Mild or definite reactions were noted in 9.6 per cent. of the children who were 7 years of age and in 43.3 per cent. of those who were 14 years of age.

It was emphasized that a positive Moloney test did not always mean that a reaction to the immunizing material would follow, but 79 per cent. of the children who had reactions to toxoid had had positive Moloney tests. There was no evidence that the positive Moloney test indicated an immunity of the patient or that it corresponded to a Schick pseudoreaction. Positive Moloney reactions were equally common among males and females and in children of large or small families, but were more frequent in patients living in urban centers than in rural districts. It was thought likely that an allergic condition arising from contact with the diphtheria bacillus accounted for a patient's positive reaction to the injection of diluted toxoid. The author concluded that all school children and older individuals who require immunization against diphtheria

should have Moloney tests first to determine their sensitivity to the material.

In a comparison of the results of Moloney and Schick pseudoreactions on 212 nurses and domestic workers, M. Mitman (*Ibid.* 35: 512 (Dec.) 1935) observed that the reactions corresponded exactly. As a result, the Moloney test was not thought to be necessary, especially since the Schick pseudoreaction also acted as a control for the true Schick test. The author agreed that the response of a patient to the Moloney test depended upon an allergic response to certain products in diphtheria bacilli and positive reactions usually indicated that a patient would have a severe reaction to the immunizing material. However, a negative Moloney test or a negative Schick pseudoreaction did not always insure a person's freedom from reaction to the toxoid materials.

An immunizing material which gives less reaction in the older age groups is *toxoid-antitoxin floccules* which is made from the flocculation resulting from the mixture of toxoid and antiserum obtained from horses. Recently, J. Y. Sugg (*Am. J. Hyg.* 22: 398 (Sept.) 1935) employed human serum for the preparation of the toxoid-antitoxin floccules. The injection of the floccules prepared in this manner lead to fewer reactions than with the previously described material. Persons immunized by this method developed relatively large amounts of antitoxin but only a small quantity of antibacterial substances. The author did not think that this human toxoid-antitoxin floccule material was necessary or practical as an immunizing material because the number of adults requiring immunization is relatively small and for this group a division of dosage of the regular material may be employed with safety to avoid severe reactions.

It has been assumed that very young infants who have retained their passive immunity obtained *in utero* do not develop active protection from injections of diphtheria toxoid as well as older infants. This was demonstrated by J. Greengard and H. Bernstein (J. A. M. A. 105:341 (Aug. 3) 1935) by comparing the Schick reactions of 2 groups of infants and their reaction to the immunization treatment. Schick tests were repeated 1, 3, 6, 12 and 18 months after treatment. Young infants, 1 month to over a year of age, who had not yet developed positive Schick reactions, were treated with diphtheria toxoid and after a few months negative skin reactions were obtained in only about 67 per cent. of the group. Infants who were positive before the treatment was given became Schick-negative in 88 per cent. of instances. The authors concluded that the presence of antitoxin in the blood of the infants who had retained their passive immunity interfered with active immunization and that preliminary Schick tests should be made on such patients before toxoid is given.

The degree of immunity produced by the injection of diphtheria toxoid in different volumes of normal saline solution was observed by P. Hartley (Brit. J. Exper. Path. 16:468 (Oct.) 1935). He noted that experimental animals became much more rapidly immune and developed higher degrees of immunity when the same dose of diphtheria toxoid was injected in 5 c.c. of normal saline rather than in 0.5 c.c. of normal saline solution. Although the experiment has not been attempted in human patients, Hartley was inclined to believe that the effect of immunization was dependent upon the rate of absorption and elimination of the antigen. The dilution of the toxoid with normal saline solution apparently prolonged the absorption of the antigen over a considerable period.

The advantages of *simultaneous immunization* against *diphtheria* and *smallpox* are well recognized, especially for mass immunizations. C. S. Stern (Am. J. Pub. Health 25:1034 (Sept.) 1935) has treated 100 children ranging from 1 to 10 years in age by injecting 1 c.c. of alum toxoid in one arm and vaccinating against smallpox on the other. In 2 instances a slight rise in temperature occurred on the evening of the day of the treatment. One child had a slight reaction at the site of the injection of the alum toxoid and 1 child developed a vomiting spell on the day following the treatment. These reactions were mild and produced no ill effects. It was found that 95 per cent. of the group developed negative Schick reactions and 98 per cent. had successful vaccination "takes." It seemed apparent the simultaneous immunization did not impair the effectiveness of either antigen and the method was safe and practical.

The occurrence of *diphtheria in Schick-negative patients* has been the subject of considerable discussion during the last few years. Occasionally the test has not accurately indicated the quantity of antitoxin circulating in the blood. Antitoxin titrations of blood serum of Schick-negative children were made recently by C. N. Leach and G. Pösch (J. Immunol. 29:367 (Nov.) 1935). A group of 215 susceptible children between the ages of 2 and 9 years were given 3 injections of formol toxoid and 9 to 32 weeks later Schick tests were performed. About 91 per cent. were found to be negative and of this group of 196 Schick-negative children the blood antitoxin titer was less than 0.01 units per c.c. in 14.3 per cent. In 3 children there was less than 0.0005 units of antitoxin per c.c.

**Diphtheria Carriers.**—The necessity of detection, isolation and treatment of diphtheria carriers in a community has been questioned by M. Kaiser and A.



Lode (Arch. f. Kinderh. 107: 40, 1935). They obtained nose or throat cultures from school children twice a week for a period of 2 years. A very large percentage of the children harbored the bacilli for a short time and only 2 to 30 per cent. of the children in the different schools were entirely free from diphtheria bacilli over a relatively long period of time. An increase in the number of carriers was often followed within a month by the outbreak of diphtheria in the community. However, the detection of the carriers in a community was thought to be of very little value in reducing the morbidity rate because the incidence of clinical diphtheria seemed to depend primarily on factors of individual susceptibility.

**Methyl violet (pyoktanin)** has been used with success in ridding patients of diphtheria bacilli by L. Bernecker (Kinderärztl. Praxis 6: 437 (Oct.) 1935). One drop of a 3 per cent. water solution of this drug was instilled into each nostril and the tonsils were painted with the solution twice a day for periods of 8 days. Of a series of 126 children treated in this manner, 90 per cent. became negative, usually after 7 to 9 days of treatment. The average duration of the treatment was 8 to 21 days. Patients with scarlet fever associated with the diphtheria and those with otitis media were the most difficult to rid of the diphtheria bacilli. Healthy carriers, 15 in number, required an average of 9 days of treatment to free them of the bacilli.

## FEEBLEMINDEDNESS IN CHILDREN

By ROBERT A. LYON, A.B., A.M., M.D.

**Etiology.**—A survey of 300 patients of the feeble-minded class in respect to the etiology of the condition was made recently by C. A. Patten and R. A. Matthews (Arch. Neurol. and Psychiat. 34: 61 (July) 1935). About 83 per cent. of this group had intelligence quotients of less than 50, and about one-half of the group had definite neurologic symptoms and signs such as abnormal reflexes, spasticity, or disturbances of sensation. The children with neurologic signs did not differ materially from those without neurologic signs as far as their mental defects were concerned. The mental deficiency seemed to be the result of some uniform pathologic change in the nervous system and the neurologic defects which were frequently encountered in the feeble-minded patients were apparently manifestations of more extensive developmental defects. Only about 4 per cent. of the group had neurologic conditions which could be ascribed to

postnatal influences. The influence of *trauma at birth* in causing mental retardation was more difficult to determine, but it seemed that cerebral injury from a difficult labor which often caused a monoplegia or hemiplegia was not a definite etiologic factor in the production of mental deficiency. It was considered possible that *anoxemia at birth* could cause destruction or injury to the brain and result in retarded mentality. The patients with hydrocephalus were generally of higher intelligence levels than the average of the group, and syphilis was not thought to be of much significance as an etiologic factor in the production of feeble-mindedness or of neurologic abnormalities. It was concluded, therefore, that the majority of retarded children had some *structural defects of the brain* which were the result of arrested development *in utero*.

The influence of *endocrine disturbances* on the mental development of 958

children was investigated by M. B. Gordon and L. Kuskin (*Endocrinology* 19: 561 (Sept.-Oct.) 1935). Only 666 of this group were mentally retarded and of the retarded group about 40 per cent. had some evidence of an endocrine disorder such as a childhood myxedema, hypothyroidism, adiposogenital dystrophy in boys, thyropituitary obesity, anterior pituitary deficiency, goiter, hypogonadism and gigantism. About 50 per cent. of the children with endocrine disorders were normal mentally and the other 50 per cent. had intelligence quotients of less than 80. Mental retardation was noted with greatest frequency in association with childhood myxedema, hypothyroidism and pituitary obesity, and least frequently in association with anterior pituitary deficiencies of growth and in goiter. Mental retardation associated with hypothyroid disturbances occurred frequently in the first 2 years of life, while those associated with pituitary disturbances occurred later. It was impossible to conclude definitely that endocrine disease had any etiologic bearing on mental deficiency.

In the *treatment* of 155 children with some endocrine disturbance, M. B. Gordon, L. Kuskin and J. Avin (*Ibid.* 19: 572 (Sept.-Oct.) 1935) found that the symptoms of endocrine disturbance improved with glandular therapy but that mental retardation without an abnormal endocrine condition showed no changes with the treatment. The therapy included the administration of desiccated **thyroid and pituitary glands**, the treatment of chronic disease, the institution of proper diet, educational measures and the improvement of social conditions. A combination of glandular extracts was often more beneficial to the patients than the use of a single glandular product alone.

**HYDROCEPHALUS.**—*Treatment.*—The treatment of hydrocephalus

by **x-ray irradiation** was tried in a group of 55 patients by E. von Lederer (*Arch. f. Kinderh.* 106: 31, 1935). About 42 per cent. showed definite improvement, and this group was composed chiefly of patients who had overproductions of cerebrospinal fluid. When the hydrocephalus was due to an impaired absorptive mechanism, the results of x-ray therapy were less favorable. No beneficial effects on the mental retardation were observed in either group.

The destruction of the choroid plexus by electrical coagulation has been advocated by T. J. Putnam (*Arch. Pediat.* 52: 676 (Oct.) 1935) in the treatment of hydrocephalus. A specially designed instrument was introduced through a trephine opening of the skull, inserted through the cortex into the ventricle and the choroid plexus coagulated by bipolar current. The procedure has been used 43 times in 22 patients. Seven of these patients have died in the hospital, 9 have survived for a period of 4 to 15 months and 5 of this group are in satisfactory physical and mental condition, 2 are improved and 2 have shown no change in their progressive mental deterioration. At first, it was the tendency to perform this operation on the most severe cases of hydrocephalus, but in a recent series of 10 patients who were selected more carefully, operation was performed earlier and only 1 hospital death has occurred in the group. This method of **electrocoagulation of the choroid plexus** seemed to promise better results in relieving intracranial pressure than other types of treatment previously attempted.

**MONGOLIAN IDIOCY.**—Apparently mongolism is not as rare in the negro race as was once supposed. In a review of the subject by A. Gesell (*J. A. M. A.* 106: 1146 (Apr. 4) 1936), 32 negro children with this condition were found to have been reported in the medical literature, including 1 in a colored

infant, 13 months of age, which he had observed. There have been 5 reported in the Chinese race, more than 6 in the Japanese, 1 in the Hindu, and 1 in West Indian races. From the replies to a questionnaire sent to 56 institutions in the United States, including hospitals and schools, the author learned that a

clinical diagnosis of mongolism had been made in 115 negro children and in 2335 white patients. It was his conclusion, therefore, that mongolism occurred rather frequently among negroes and there was no reason to believe that any racial characteristics of the negroes conferred upon them an immunity to this type of idiocy.

## DISEASES OF THE GENITOURINARY SYSTEM IN CHILDREN

By WALDO E. NELSON, A.B., M.D.

### HEMATURIC NEPHRITIS.—

**Etiology.**—A study designed to determine what differences, if any, exist in the nature of the preceding infection and the incidence of acute glomerulonephritis in hospital practice in New York as compared with hospital practice in the south has been conducted by D. Seegal and B. C. Seegal and J. D. Lyttle (J. A. M. A. 105:17 (July 6) 1935). The case frequency of the disease in the two groups of hospitals was found to be closely parallel. Likewise, the age group of the northern and southern cases was similar. About 50 per cent. of the cases occurred before the age of 10 years and 70 per cent. before the age of 21. The type of infection preceding acute glomerulonephritis was much the same for the two groups. This preceding infection was usually of the type associated with tissue invasion by the hemolytic streptococcus. Most of these infections were associated with the upper respiratory tract as, for example, acute cervical lymphadenitis, peritonsillar abscess and acute mastoiditis. In a few instances preceding infections caused by the pneumococcus and the staphylococcus were noted. Elsewhere, these authors have shown that while the medical admission rate for acute glomerulonephritis was similar in 24 hospitals in 4 latitude regions, the case frequency for two other

diseases, chiefly of hemolytic streptococcal origin, scarlet fever and rheumatic fever, was less in the south than in the north. The authors suggest that if all three diseases are related to a preceding hemolytic streptococcal infection, there must be factors other than a specific hemolytic streptococcus to account for the lack of parallelism between the geographic distribution of these three diseases.

### NEPHROSIS.—*Treatment.*—

M. W. Dick, E. Warweg and M. Andersch (J. A. M. A. 105:654 (Aug. 31) 1935) have not only been unable to confirm the previous good reports of the use of *acacia* in the treatment of nephrotic edema, but have found that its use over a period of time may be attended with *deleterious effects*. They did find that the use of *acacia* intravenously exerted a transient or slight effect on the edema of nephrosis. However, continued use of *acacia* led to a marked lowering of the serum protein and to the development of an enlarged, tender liver. When *acacia* therapy was discontinued, the serum protein tended to remain low; the liver, however, slowly resumed its normal size. *Acacia* was found in deposits of edema fluid in 2 patients and in one of these coming to necropsy, appreciable amounts of *acacia* were found by chemical analysis in the liver, and there was evidence by

microscopic examination of deposits in the bone marrow, lymph nodes, lungs, kidneys, spleen and liver. The administration of acacia intravenously in equivalent doses to dogs produced a marked lowering of the total serum protein. This reduction in protein did not appear to be a simple dilution effect. When the daily administration of acacia was discontinued, the serum protein values of the dogs returned to normal much more rapidly than was observed in the nephrotic children.

**RENAL RICKETS.—*Differential Diagnosis.***—An instance of renal rickets in which there were increased amounts of parathyroid hormone in the blood antemortem and in which 4 enlarged parathyroids were demonstrated postmortem, is reported by D. H. Shelling and D. Remsen (Bull. Johns Hopkins Hosp. 57:158 (Sept.) 1935). The clinical symptomatology, the x-ray appearance of the bones, the metabolism of the calcium and phosphorus, as well as the presence of increased amounts of parathyroid hormone in the blood, were indistinguishable in this instance from those seen in *osteitis fibrosa* of the osteoporotic type which is complicated by impairment of renal function. The differential diagnosis between the two diseases is based largely on the chronologic history of onset of renal failure, on the presence or absence of nephrolithiasis or nephrocalcinosis (present in hyperparathyroidism and absent in renal rickets), and on the presence or absence of congenital anomalies of the genitourinary tract. The authors suggest the hypothesis that the impetus for the secondary hyperplasia and hypersecretion of the parathyroids is the phosphate retention, and that the demineralization of the skeleton in renal rickets is due, among other factors, to the necessity of excreting the retained phosphate as the insoluble salt of calcium in

the bowel, to the compensatory secretion of increased amounts of parathyroid hormone and possibly also to the chronic acidosis.

**RENAL CALCIFICATION.**—A. M. Butler, J. L. Wilson and S. Farber (J. Pediat. 8:489 (Apr.) 1936) report what they believe to be an original description of the association of a clinical syndrome and pathologic condition. The clinical syndrome is characterized by: (1) persistent dehydration in the absence of excessive diarrhea and vomiting and in the presence of adequate food, salt and fluid intake; (2) a persistent hyperpnea associated with a sustained elevation of the serum chloride concentration and reduction of the serum bicarbonate content; and (3) deposits of calcium salts within and adjacent to certain renal tubules. This syndrome was observed in 4 infants and 1 child, all of whom showed a strikingly similar clinical picture. Only 1 of the 5 patients had definite sclerema. Hypotonia occurred in a striking degree in 2 of the 4 infants. In each of the infants there was evidence of first, an upper respiratory infection, and, terminally, a pneumonia. While calcification occurs frequently in necrotic tissues, there was no evidence in any kidney of these infants that calcification was secondary to the degeneration of any renal element. It was noted that the calcium deposits were in locations traversed by calcium salts during normal renal function. Calcification in renal tubules has been observed in patients with dehydration, hypochloremia, and alkalosis resulting from upper intestinal obstruction. Although an alkalosis from chloride loss due to vomiting may have occurred at some time in these infants, there was no evidence of a simultaneous alkalosis and dehydration that might have contributed to calcification in the renal tubules. Since no alkali was given

to any of the patients, the calcification would not seem to have resulted from alkaline therapy. The absence of any histologic evidence of parathyroid hyperplasia or of calcification elsewhere in the body suggests an etiology of the renal calcification other than that of hyperparathyroidism.

**LOWER URINARY TRACT INFECTION.**—*Diagnosis.*—After a systematic study of the urine from 694 infants and children who were patients in a children's orthopedic hospital, A. B. Hepler and R. T. Scott (J. A. M. A. 105:499 (Aug. 17) 1935) conclude that only catheterized urine should be used for the determination of pus cells and, furthermore, the number of white cells in a urine properly collected is no indication either of the kind or severity of urinary tract disease. In centrifuged, voided urine the authors demonstrated pus in 99 per cent. or in the urine of 687 children, in contrast to only 13 per cent. or in the urine of 99 children from centrifuged, catheterized urine. Perhaps of more importance are their findings in uncentrifuged urine. In the uncentrifuged, voided urine, pus was demonstrated in 246 or 36 per cent., in contrast to only 64 or 9 per cent. in the uncentrifuged catheterized specimens. Of these 64 children, 26 were shown to have had demonstrable urinary tract disease. Only 10 of the 26 children were admitted for diagnoses and treatment of a urologic condition and only 9 had subjective symptoms directly referable to the urinary tract. The amount of pus in the urine of the children with demonstrable urinary tract disease varied from an occasional pus cell (less than 1 per high dry field) to over 20 per high dry field. Two children with urinary tract disease had no demonstrable pus in their urine, while 11 of this group had not more than 5 pus cells per high dry field. Exactly similar lesions

were shown to exist with white cell counts that varied from less than 1 per high dry field to more than 20 per high dry field.

On the basis of these observations, the authors feel that any persistent or recurrent *pyuria*, no matter what the cell count, should be taken as a criterion for a complete renal study. Since many urologic lesions in children have no or misleading symptoms, they contend that there is less evil in making an unnecessary examination than in failing to make an early diagnosis. They also made a study of the comparative value of fresh smears and cultures in determining the type of infection. One hundred and eighty-three catheterized urines were examined both by smears and by cultures. In these examinations the smear and culture agreed in 170 instances or in 92 per cent.

The more common *indications* for *urologic examination* in infants and children are listed by M. F. Campbell (J. Pediat. 8:748 (June) 1936) in the order of their incidence: chronic *pyuria*, disturbances of urination, pain or tumor along the urinary tract, hematuria not due to an acute nephritis, and persistence of acute urinary infection. The various causes of *pyuria* and hematuria are so well illustrated by schematic outlines in the author's article that they are reproduced here. (See Figs. 1 and 2.)

*Treatment.*—*Ketogenic Diet.*—In a review of his experience with the ketogenic diet in the treatment of urinary infections, H. F. Helmholz (*Ibid.* 105:778 (Sept. 7) 1935) emphasizes that the successful use of this form of therapy is dependent upon the bactericidal action of beta-oxybutyric acid at a certain degree of acidity. The limit at which this action occurs has been shown to be 0.5 per cent. beta-oxybutyric acid at a pH below 5.5. If the concentration

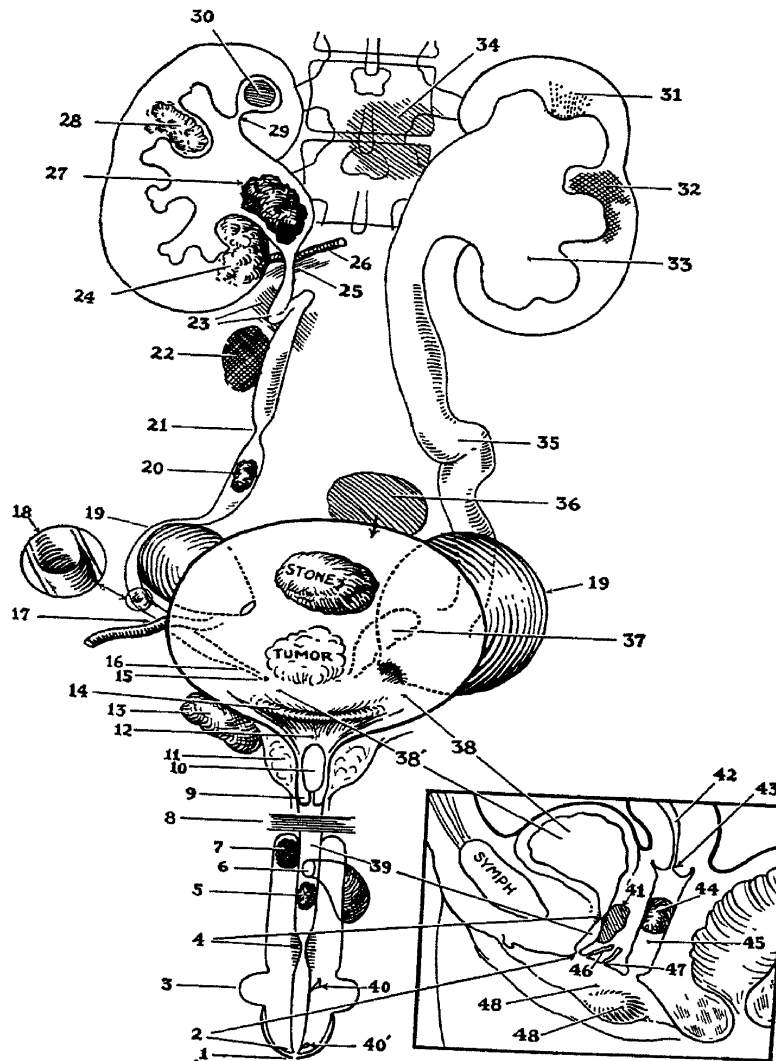


Fig. 1.—Direct and indirect causes of pyuria. These lesions, the clinical manifestations of which so commonly lead to inadequate diagnosis of pyelitis, either acute or chronic, can be identified only by a thorough urologic examination. 1, Stenosis of prepuce; 2, stenosis of urethral meatus; 3, paraphimosis; 4, urethral stricture; 5, urethral stone; 6, urethral diverticulum; 7, valves of posterior urethra; 8, cowperitis; 9, congenital prostatic abscess; 10, hypertrophy of verumontanum; 11, prostatitis; 12, contracted bladder neck; 13, periprostatitis or pelvic suppuration; 14, mucosal fold at bladder outlet; 15, trigonal curtain; 16, stricture of ureteral meatus; 17, ureterocele; 18, congenital ureteral values; 19, ureteral obstruction by diverticulum compression; 19', diverticulum; 20, ureteral stone; 21, ureteral stricture; 22, periureteritis; 23, periureteral phlegmon or stricture; 24, renal tumor; 25, ureteropelvic junction tuberculosis; 26, aberrant vessel obstruction of upper ureter; 27, pelvic stone; 28, renal nephrosis; 29, stricture of calyceal outlet; 30, calyceal stone; 31, pyelonephritis; 32, pyotract; 33, "pyelitis"; 34, infected hydronephrosis; 35, hydroureter; 36, pericystic abscess rupturing into bladder; 37, seminal vesiculitis; 38, neuromuscular vesical disease; 38', cystitis; 39, urethritis; 40, folliculitis (Littre); 40', folliculitis (Morgagni); 41, periurethritis; 42, endometritis; 43, cervicitis; 44, foreign body in vagina; 45, vaginitis; 46, skenitis; 47, folliculitis of introitus; 48, bartholinitis. (M. F. Campbell: J. Pediat.)

of the acid is increased and the  $pH$  decreased, there is an increase in the bactericidal power of the urine. It has also been shown that bactericidal action occurred below the minimal concentration when the  $pH$  of the urine is lowered and is present at a  $pH$  above 5.5 if the

dried. This dried paper becomes yellow and is turned red in a solution of  $pH$  above 5.5. Consequently it is necessary only that the urine shall not be capable of turning the test paper red.

Inasmuch as there is no satisfactory chlorimetric measure for beta-hydroxybutyric acid and since there is a fairly constant ratio be-

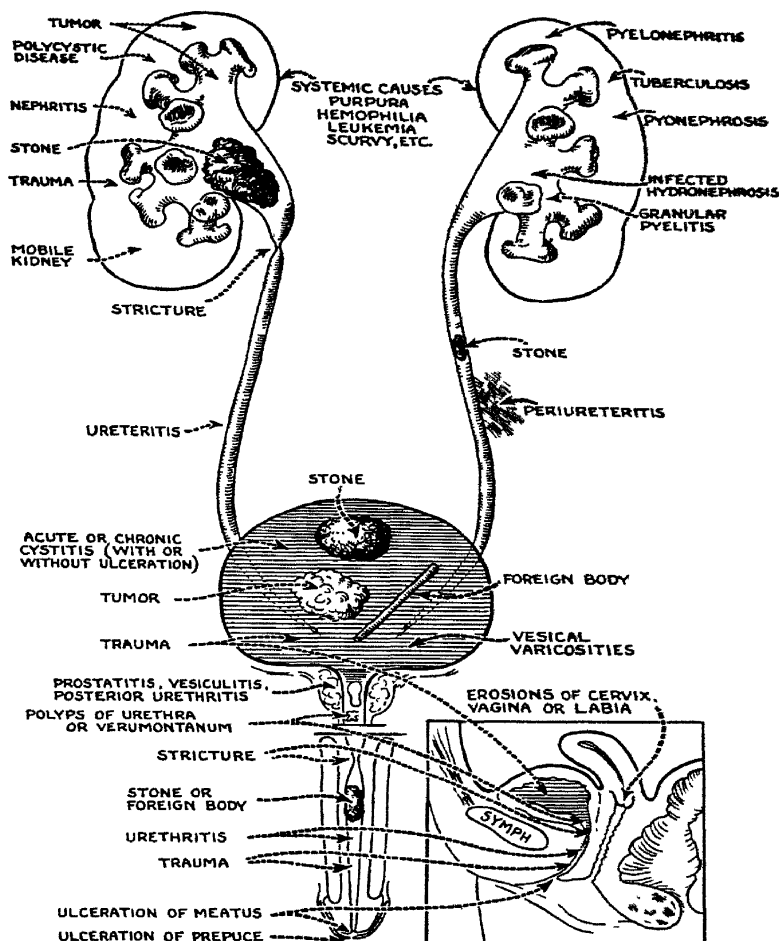


Fig. 2.—Causes of hematuria. Only by urologic examination, surgical exploration or autopsy can most of these lesions be identified. (Campbell: J. Pediat.)

concentration of the beta-oxybutyric acid is increased considerably. A test for the concentration of beta-oxybutyric acid is detailed and the use of chlorphenol red paper for the determination of a  $pH$  below 5.5 is explained as follows:

Whether or not the  $pH$  value of urine is greater or less than 5.5 is determined by the use of chlorphenol test paper. This is prepared by soaking a good grade of filter paper in an aqueous solution of chlorphenol red, of a concentration of 0.04 per cent., which is then

tween the concentration of diacetic acid and beta-hydroxybutyric acid in the urine, over a fairly wide degree of ketosis, Osterberg and Helmholtz adopted a simple procedure for determining the concentration of diacetic acid and, indirectly, of beta-hydroxybutyric acid as follows:

To 800 mg. of ammonium sulphate in the ordinary Nessler comparison tube (tall form) graduated at 50 c.c. is added 3 drops of concentrated ammonium hydroxide (0.15 c.c.), 2 drops (0.10 c.c.) of a 5 percent. solution of sodium nitroprusside, and 1 c.c. of the urine

to be examined. This is allowed to stand 6 minutes at a room temperature of approximately 25° C. (77° F.). The reaction product is then quickly diluted with water to the 50 c.c. mark and mixed. This solution is immediately compared with the standard. If the color of the unknown is deeper than that of the standard, the concentration of beta-hydroxybutyric acid is greater than 0.5 per cent. If the color is lighter, the reverse is true. The standard is prepared by adding 4.0 c.c. of a solution, containing 2 parts of 0.04 per cent. solution of phenol red and 1.4 parts of a 0.04 per cent. solution of bromthymol blue, to 46 c.c. of phosphate buffer of pH 8.0. The standard retains its color for a considerable time, but a fresh standard may be prepared very easily if only an occasional determination is to be made.

Helmholz feels that the ketogenic diet is a useful method for treating urinary infections resistant to alkalinization, diuresis and urinary antiseptics. In cases in which urinary anomalies are associated with stasis, a temporary and often permanent cure of the infection is achieved in those cases in which a pH of less than 5.5 and a concentration of 0.5 per cent. of beta-oxybutyric acid can be maintained in the urine for a period of time. Nephrolithiasis and impaired renal function are serious handicaps to the success of this type of treatment.

It is becoming increasingly evident that a common cause of chronic pyelitis in infants and children is obstruction at the internal orifice of the bladder resulting from congenital valves or contractions. In this respect the series of cases of obstruction of this type treated by transurethral removal by J. R. Caulk (J. Missouri M. A. 32:461 (Dec.) 1935) is of particular interest. In 13 of 16 such operations the author has secured perfect results and 2 were decidedly improved. In the 1 case in which there was no improvement there was an associated spina bifida.

**VULVA.—Adhesions.**—According to P. Nowlin and J. R. Adams (J.

Pediat. 8:200 (Feb.) 1936), partial or complete atresia of the vulva due to adhesions between the labia minora is more frequent in female infants than generally suspected. In 6 of the 8 instances observed by the authors there were secondary urinary disturbances. These were manifested by interruption of the stream, tenesmus and frequency. In 1 instance, a chronic pyelocystitis of 9 months' duration was apparently due to this form of obstruction. There was residual urine in the bladder and in the vagina due to the obstruction. The treatment is simply that of separation of the labia minora either by gentle manipulation or by the use of a probe.

**VAGINITIS.**—When the *etiologic diagnosis* of vulvovaginitis is not apparent, A. C. Ruys (J. A. M. A. 105: 862 (Sept. 14) 1935) recommends that bacterial cultures be employed. For the isolation of *gonococci*, she used Levinthal-agar plates with 20 per cent. ascitic fluid and a modified blood-water-agar medium of Bieling, which is prepared as follows: Blood is drawn from the vein of a horse into an equal quantity of distilled water and kept at 60° C. for 30 minutes. Two parts of this fluid are mixed with 3 parts of 2 per cent. nutrient agar.

For the examination of smears, Ruys states that *van Loghem's Gram method* is superior. The technic of this method is as follows:

The material is evenly and thinly spread on a slide and fixed by heat. Then it is stained with carbol-gentian violet for 5 minutes, being warmed at minute intervals to nearly 37° C. This stain is poured off and the film is treated with compound solution of iodine for 45 seconds. The iodine is poured off and the film decolorized intensely in 96 per cent. alcohol for exactly 30 seconds. If portions of the film are too thick they must be removed mechanically during decolorization. Next the film is rapidly rinsed in water and counterstained with an aqueous solution of fuchsin.



With this method, most cocci from the vagina are Gram-positive, while gonococci, and only occasionally some other cocci, are Gram-negative. Ruys has attempted without success to change the gonococci into Gram-positive ones, nor was she able to change the Gram-positive cocci from the vagina of children into gonococci. She considers that there is no reason to believe that gonococci can become Gram-positive. In all patients with gonorrheal vulvovaginitis, she was able to isolate gonococci from the rectum.

**Treatment.**—Good results from the estrogenic treatment of *gonorrheal vaginitis* are reported by L. E. Goldberg, C. L. Minier and E. L. Smith (J. Pediat. 7:401 (Sept.) 1935). They employed **amniotin** in the treatment of 17 patients with vaginitis; 16 of these cases had a gonorrheal infection, and 1 had an infection of nonspecific origin. Fourteen of the 16 patients with the specific type are reported as cured and have shown no recurrence in a period varying from 129 to 271 days. There was a recurrence of the infection in the nonspecific case. The author thus concludes that this estrogenic preparation provides an efficacious method for the treatment of gonorrheal vaginitis. Amniotin was administered both orally and hypodermically. The authors prefer the oral method but state that either the oral or hypodermic method is preferable to and more effective than the exclusive topical method. Their dosage of the drug, when administered orally, varies from 100 to 400 rat units daily. They are in agreement with other investigators who attribute the benefit with this form of treatment to the change of the immature vaginal lining of a few layers of epithelial cells to that of the adult type with 20 to 30 layers and cornification of the outer ones.

As a result of their observations, R. M. Lewis and E. L. Adler (J. A. M. A. 106:2054 (June 13) 1936) consider the use of **vaginal, estrogenic suppositories** the most effective method for the treatment of *gonorrheal vaginitis in children*. They have used a vaginal suppository containing 1000 International units which was inserted into the child's vagina each night. No vaginal washes or applications were used except that the external genitalia were cleaned as necessary. Clinical improvement, cessation or great diminution of discharge was nearly always noted after from 14 to 18 days of treatment. The reaction of the vaginal secretion was changed from neutral or alkaline to acid, which the authors believe to be the major factor in eliminating the gonococcic infection. The acidity of the vaginal secretion is easily measured and provides a sure guide by which it may be determined whether or not the dosage is adequate. Of 33 consecutive cases of gonorrheal vaginitis in children treated with estrogenic suppositories, negative smears were obtained in 30 instances in an average of 20.7 days. In 5 children there were recurrences. No ill effects were noted from the treatment.

An unfavorable experience in the treatment of *gonorrheal vulvovaginitis* in children with ovarian follicular hormone is reported by J. T. Witherspoon (Am. J. Dis. Child. 50:913 (Oct.) 1935). Ten children with gonorrheal vulvovaginitis were treated with ovarian follicular hormone (**amniotin**) without success. There was not only a persistence of vaginal discharge, but the gonococci failed to disappear. Several disadvantages of this method of therapy are pointed out, such as the harmful effect on the immature ovary; the fact that cervical infection in addition to vaginitis is a common attendant and a focus for continuing the disease; the unpleasant

features of the daily hypodermic injection; the occasional unfortunate secondary sexual changes, such as enlargement

of breasts, vulval hyperemia and hypertrophy; and, lastly, the high cost of this method of therapy.

## HEART DISEASE

By ROBERT A. LYON, A.B., A.M., M.D.

**CONGENITAL HEART DISEASE.**—The subject of congenital heart disease has been reviewed recently by S. McGinn and P. D. White (New England J. Med. 214:763 (Apr. 16) 1936). Among 7500 necropsies, definite congenital heart lesions were found in 67 instances or 0.9 per cent. of the entire number. About one-third of the patients were less than 1 year of age.

In a group of 41 cases occurring during the last 15 years, the most common congenital *cardiac defect* was patency of the ductus arteriosus, occurring alone in 4 and in conjunction with other lesions in 5 instances. Defects in the auricular septum occurred in 7 instances, defects of the interventricular septum in 6, congenital idiopathic hypertrophy in 3, a 3-chambered heart in 1, and a 2-chambered heart in 1 case. Abnormalities of the coronary vessels were noted in 5 cases and of the valves in 13 instances. Valvular defects included bicuspid aortic valves in 7 cases, a bicuspid pulmonary valve in 1, 4 cusps of the pulmonary valve in 2, and in 1 instance each, a single mitral leaflet, pulmonary stenosis, and variations of the size of the aortic cusps.

An accurate clinical diagnosis was made in 7 patients of the group of 41; 4 of these were adults and 3 were infants less than 1 year of age at the time the diagnosis was made. The lesions diagnosed were idiopathic hypertrophy, interventricular defects, pulmonary stenosis and the tetralogy of Fallot. In 5 other patients, the type of congenital defect was suspected before death, so

that a total of 12 patients or 29 per cent. of the series had sufficient clinical evidence to suggest the anatomic defect. In 3 other instances the clinical diagnosis of congenital heart disease was made without the nature of the defect being ascertained. In 25 patients congenital heart disease was not suspected. The percentage of accurate diagnoses was greater in the last few years than in the earlier periods, especially in those patients who had been examined by physicians experienced in cardiology. Some of the lesions, such as abnormalities of the coronary vessels and heart valves, gave no clinical symptoms and, if these patients were eliminated from the series, a correct diagnosis was found to have been made in 85 per cent. of instances. It was the opinion of McGinn and White that there were sufficient means today of diagnosis of patent ductus arteriosus, Interventricular septal defects, idiopathic congenital hypertrophy, the tetralogy of Fallot, coarctation of the aorta, the persistence of a right aortic arch, coronary artery anomalies, cor biatriatum trioculare and interauricular septal defects with or without mitral stenosis.

Of these lesions the last 3 are the least common. *Anomalies of the coronary arteries* were found to cause the patient some distress on exertion, led to cardiac enlargement, and in the electrocardiograms variations were observed in T waves similar to those associated with coronary occlusion or myocardial infarction. A *3-chambered heart with 2 auricles and 1 ventricle* produces a typi-

cal "water bottle" shadow in the x-ray picture and electrocardiographic evidence of intraventricular block. *Inter-auricular defects* alone are characterized by terminal cyanosis, an enlargement of the pulmonary artery, hilus shadows and the right ventricle in the x-ray picture, a right axis deviation in the electrocardiogram, and paradoxical embolism arising from the passage of emboli from the systemic system directly through the auricular defect back into the systemic circulation.

In a similar survey made during the past year, an effort was made to correlate clinical findings with autopsy reports. In a series of 13,115 autopsies, reviewed by C. B. Leech (*J. Pediat.* 7:802 (Dec.) 1935), which were performed over a period of more than 40 years at the Johns Hopkins Hospital, 170 cardiac anomalies were recorded, an incidence rate of 1.29 per cent. Including instances of delayed closure of the foramen ovale and ductus arteriosus, and a few cases not analyzed, the incidence rate would have been 1.48 per cent. A group of 75 definite congenital anomalies were reported. More than half of this series of patients had died before the age of 1 year, and only 11 reached the age of 17 years or more. Males constituted 61 per cent. of the group, premature infants made up 13.3 per cent. of the series, most of which had defects such as the failure of closure of the ductus arteriosus or foramen ovale which probably was the result of under-development of the infant.

*Cardiac enlargement* had been diagnosed clinically in 57.3 per cent. of the group but in about one-fourth of this number autopsy did not substantiate the finding. The most common anatomic lesion in the group with cardiac enlargement was patency of the interventricular septum. Hypertrophy of the right ventricle was most prominent in patients

with stenosis of the pulmonary artery, aortic stenosis and other lesions combined with foramen ovale and interventricular septum defects. Idiopathic hypertrophy was noted in 5 patients. Permanent cyanosis occurred in 22 per cent. of the group, delayed or intermittent cyanosis (*cyanose-tardive*) in 25 per cent. Clinical cyanosis occurred in only 75 per cent. of those patients who had cardiac lesions which are usually thought to give this symptom, and transient cyanosis was present clinically in only 40 per cent. of those with cardiac lesions supposed to produce that symptom. *Patency of the ductus arteriosus* occurred in 36 per cent. of the group, but it was much more frequently found in autopsies of infants under 4 months of age, so that its importance as a distinct cardiac anomaly could not be estimated.

From a clinical standpoint alone the incidence of congenital cardiac defects was found by G. Stancanelli (*Pediatrics* 43:1105 (Oct.) 1935) to be lower than the above figures indicate. Among 17,257 children visiting an out-patient clinical in Naples during a period of 8 years, heart disease of all kinds occurred in 0.6 per cent., but more than a third of this group, or 0.23 per cent. of the total number, were thought to have had congenital heart disease. Including a series of congenital heart patients seen elsewhere, the author reported a total number of 77 children with clinical signs of cardiac anomalies. Males were twice as common as females in this group, and the most common symptom of both sexes was cyanosis, noted in 30 patients. The most frequent diagnoses were patency of the interventricular septum in 30 patients, pulmonary stenosis in 6, patent ductus arteriosus in 5, and single cases of several other lesions.

The symptoms and prognosis of patients with *coarctation of the aorta* differ with the position of the constriction. A classification of this lesion into adult and infantile types has been suggested by E. N. Ballantyne (Am. J. Dis. Child. 50:642 (Sept.) 1935) and he reported 3 cases of coarctation of the aorta of the infantile type. When the constriction of the vessel is opposite or distal to the entrance of the ductus arteriosus it should be considered as an adult type. In such instances there is an interference of the flow of blood into the descending aorta either by way of the ductus arteriosus or by the aortic arch, but during fetal life collateral circulation develops gradually and the newborn infant has the compensatory mechanism to cope with his new environment when the pulmonary circulation is established. In the fetal types of coarctation, the constriction is proximal to the entrance of the ductus arteriosus. During fetal life the flow of blood is unimpaired because the ductus carries the blood to the descending aorta with the aid of the right ventricle and without the necessity of collateral circulation, but when the child is born, the development of pulmonary circulation throws an extra burden upon the right heart and the child often succumbs. Since the position of the ductus arteriosus, as well as constriction is variable, the authors thought it wise to employ the classification of infantile or adult types of coarctation, depending upon the relation of these structures or anomalies to each other.

Among a group of congenital cardiac anomalies in infants reported by F. A. Hemsath, M. Greenberg and J. H. Shain (*Ibid.* 51:1356 (June) 1936) was a case of *accessory ventricle*. Symptoms of cyanosis and dyspnea had occurred when the infant was 6 weeks old and the x-ray showed considerable enlargement, especially to the left, but the heart

was entirely normal to auscultation. The child died 2 weeks later and at autopsy an accessory left ventricle was found which opened into the regular left ventricle, near the posterior cusp of the mitral valve. No other reports of such a condition could be found in the literature although diverticula and finger shaped projections from the cardiac apex have been observed in a few instances.

Persistent *truncus arteriosus communis* occurred in an infant observed by A. Roos (*Ibid.* 50:966 (Oct.) 1935) and this was the sixth report of such a condition in the literature. The common findings of this group of patients were cyanosis shortly before or after birth, and occasionally murmurs, systolic in time, heard best in the second interspace to the left of the sternum, or in the mitral region. The anatomical criteria summarized by the author for such a diagnosis were: (1) only 1 trunk emerging from the heart; (2) 4 semi-lunar cusps; (3) the single vessel performing the functions of the aorta and pulmonary arteries combined, usually giving branches to the systemic and coronary circulations and to the lungs; (4) a defect of the upper part of the interventricular septum; (5) a defect of the auricular septum; and (6) distortions of the origin of the truncus, either arising above the defect in the ventricular septum or from the right ventricle entirely. It was usually found that the cusps of the valves of this truncus were fixed and hard, which the author thought was a remnant of fetal development, since these valves are very bulbar and thickly packed with cells in early fetal life and gradually become thinner as the fetus grows and develops.

An instance of *congenital cardiac hypertrophy* in a young infant was observed by R. Debré, J. Marie and J. Bernard (Arch. de méd. d. enf. 39:98 (Feb.) 1936). Symptoms of dyspnea

and occasionally cyanosis in later stages were noted but the important finding was a large globular shadow of the heart in the x-ray picture. At autopsy no valvular lesions or evidence of inflammation could be discerned, but only an increase in muscular tissue without vacuolization or deposits of fat or glycogen. The authors considered etiologic factors of this type of hypertrophy of the heart to be either a disturbance of metabolism or a congenital malformation similar to the hypertrophy of the pylorus, colon, or other organs which are occasionally observed in the newborn.

*Congenital thinning* of the walls of the right anterior aortic sinus of Valsalva was reported by V. Sprenkel and H. L. Stewart (J. Lab. and Clin. Med. 21:128 (Nov.) 1935). The aortic septum had failed to divide and there was a failure of spiral rotation of the aorta, so that a mild degree of dextroposition of the aorta resulted, together with a defect of the anterior interventricular septum. The patient died at the age of 16 years with a subacute bacterial endocarditis.

The association of acquired infectious lesions with structural abnormalities of the heart is a frequent occurrence and is an important factor in the prognosis of congenital cardiac defects. An example of this kind was the patient with *patent ductus arteriosus with endocarditis* and a *terminal hemorrhagic nephritis*, observed by D. C. Hines and D. A. Wood (Am. Heart J. 10:974 (Oct.) 1935). Death occurred at the age of 18 years; at autopsy vegetations were found on the pulmonic valve and in the ductus arteriosus extending into both the pulmonary artery and into the aorta. A streptococcus viridans was the apparent cause of the bacterial endocarditis and the lesions were limited to the ductus and to the right side of the heart.

There were many pulmonary infarcts, and the nephritis, which was a hemorrhagic type, appeared to be a diffuse glomerulonephritis with focal embolic lesions. Thirty-three reports have occurred in the medical literature in which patent ductus arteriosus was complicated with pulmonary endarteritis and endocarditis.

*Congenital and rheumatic heart disease* may also be associated in the same patient, as in the case of an open foramen ovale and mitral stenosis reported by S. Gibson and A. Roos (Am. J. Dis. Child. 50:1465 (Dec.) 1935). The child was 10 years old at the time of death and it was apparent that the defect of the auricular septum was a congenital lesion and the mitral valvulitis was of a rheumatic nature. The predominant murmur heard in this patient was a loud systolic murmur in the third interspace to the left of the sternum, and the x-rays showed cardiac enlargement, a prominent pulmonary conus and increased hilar markings. The enlargement of the right side of the heart became more prominent in the x-ray pictures as the patient grew older. At necropsy there were found a wide open foramen ovale, a marked mitral stenosis and insufficiency, and involvement also of the tricuspid valve, the endocardium and myocardium. The pulmonary artery was large but the aorta was smaller than normal. Other congenital defects noted in this patient were a slight hypospadias, an incomplete coloboma of both eyes and a Meckel's diverticulum. Only 26 instances of associated defects of the auricular septum and mitral stenosis had been reported previously in the literature, and 22 of these patients were females.

**RHEUMATIC FEVER.**—*Incidence.*—The low incidence of rheumatic fever manifestations among the inhabitants of southern Florida was pointed

out by E. S. Nichol (J. Lab. and Clin. Med. 21:588 (Mar.) 1936). During a 5-year period there were only 11 patients with rheumatic joint pains or carditis among more than 8000 medical admissions to a general hospital in Miami, a rate of 0.13 per cent. No instances of chorea were seen. This rate was less than one-tenth of that reported in Boston. Of the total number of cardiac patients observed in hospital and office practice, only 1.3 per cent. in Florida were of rheumatic origin in contrast to 31.9 per cent. in New England. In some southern states where there is but little influx of visitors from the north, the manifestations of rheumatic fever are reported to be even less frequent.

The experience in Minnesota with rheumatic fever in 713 children has been related by M. J. Shapiro (*Ibid.* 21:564 (Mar.) 1936). The seasonal incidence was similar to that in other cities such as Boston, Philadelphia, and New York, with the greatest number of attacks occurring in the spring and fall months, and the lowest number in the summer months. The most common age in which the first symptoms of rheumatic fever were noted was between 5 and 6 years. A positive history of rheumatic fever was found 3 times more frequently in the families of these patients (47 per cent.) than in the families of normal children (15 per cent.).

Preceding infections were absent in about 45 per cent. of the group of children, while 14 per cent. had had a cold immediately preceding the onset of rheumatism; 4.5 per cent. had had sore throats; 2 per cent. pneumonia; 1 per cent. measles; 6 per cent. scarlet fever; 10 per cent. chorea; 0.5 per cent. had various other types of infections, such as otitis media, infected fingers or traumatic injuries immediately preceding the onset of the rheumatic fever.

A large number of children who were examined in the clinic because of pains in the legs did not have rheumatic fever. The author believed that characteristic growing pains of nonrheumatic nature were likely to occur at the time of going to bed and to be absent in the morning, and consisted of soreness of the muscles rather than localized tenderness of the joints, as in rheumatic fever.

The general health of the rheumatic patients was not as good as those with nonspecific joint pains and, of course, the former group was more apt to have other symptoms of rheumatic infection such as nose bleed, pallor, abdominal pain and fever than the children with growing pains only. More than half of the group (51 per cent.) had only 1 attack of rheumatic fever. Of the remainder who had more than 1 attack, about a fourth had recurrences within the first year, a half within a 2-year period, and by the end of 5 years, 86 per cent. of the group had had recurrences. It was thought necessary, therefore, to observe children with rheumatic fever for a period of at least 5 years in order to be sure that they were free from manifestations of the disease.

A survey of the incidence of rheumatic fever, scarlet fever and acute glomerulonephritis in various parts of North America was made by D. Seegal, B. C. Seegal and E. L. Jost (Am. J. M. Sc. 190:383 (Sept.) 1935) from statistics gathered from 24 hospitals of the number of patients admitted with these diseases during the years 1910 to 1931. The geographic distribution of the rheumatic fever and scarlet fever was somewhat similar, but the incidence of nephritis was fairly uniform in all parts of the country. The authors were inclined to believe that if the hemolytic streptococcus was the etiologic agent causing all 3 of these illnesses, the differences in the action of the organism

or in the resistance of the host might account for the variation in geographic distribution.

**Etiology.**—A study of the *bacteriologic flora* of the throats of 35 girls between the ages of 6 and 16 years, all but 1 of whom had some evidence of rheumatic fever, was made throughout the period of 1 year by A. F. Coburn and R. H. Pauli (J. Exper. Med. 62:129) (Aug.) 1935). Many of these patients carried a strain of *hemolytic streptococci* in their throats throughout the winter but the presence of this organism was not associated with any clinical manifestations of disease. Four children developed chickenpox during the year but this disease caused no exacerbation of the rheumatic symptoms. Their throat flora contained no hemolytic streptococci during the attacks of chickenpox nor was there any rise in the antistreptolysin level throughout the illness. An epidemic of influenza from which a virus was isolated did not cause exacerbations of the rheumatic fever in any of the patients, but the disease was followed by an outbreak of a streptococcus infection of the hemolytic type which caused an exacerbation of the rheumatism in 14 of the group of 17 who developed the infection. An increase in the antistreptolysin titer accompanied the exacerbation of rheumatism in these 14 patients. The streptococcus infections which followed influenza and the epidemic of streptococcus infection which occurred independently resulted in the same type of rheumatic exacerbations.

In a subsequent report Coburn and Pauli (*Ibid.* 62:159 (Aug.) 1935) stated that the occurrence of attacks of rheumatic fever seem to be independent of diet, state of nutrition, temperature, clothing, amount of rest obtained, or protection from unfavorable weather. These factors were carefully observed in a home for children with cardiac disease.

During the period of observation, however, an epidemic due to a single type of hemolytic streptococcus caused severe exacerbation in 14 of a group of 23 children. Seven of these patients who did not have exacerbation of rheumatic fever had no hemolytic streptococci in their throats. Two other children, however, who had this type of throat infection and did not develop rheumatic symptoms had no increase in the antistreptolysin of their blood.

Further studies by A. F. Coburn and R. H. Pauli (J. Clin. Investigation 14: 755, 763, 769, 783 (Nov.) 1935) have indicated that the strains of *hemolytic streptococci* obtained from rheumatic fever patients which seemed to cause exacerbations of rheumatic disease were very similar to strains of streptococci causing scarlet fever. Such organisms produced a soluble toxin and stimulated the production of a streptolysin. Other organisms of the hemolytic streptococcus type which did not have these characteristics apparently did not cause rheumatic fever activity. Attempts to immunize individuals against rheumatic fever infections by use of scarlet fever types of toxin, or the administration of scarlet fever antiserum to give passive immunity, did not seem to prevent reactivation of rheumatic infections. Rheumatic patients who developed large amounts of antistreptolysin had recurrences of their disease, while other patients who did not have increases in the titer of antistreptolysin did not develop rheumatic attacks. The rise of antistreptolysin was very closely associated with the time of onset of acute rheumatic infection. It is the author's opinion that the rheumatic process is the result of (1) infection with a toxin-producing strain of hemolytic streptococcus, which is followed by (2) the formation of antibodies by the patient which in some way affect the mesodermal structures.

The authors removed the spleen from a few patients in order to reduce the patient's antibody response but this operation did not seem to persistently reduce the amount of antibody formation nor did it influence the rheumatic activity. Following the splenectomy, several patients developed exacerbations of rheumatic fever without any increase in the antistreptolysin titer.

Evidence of a relationship between *deficiencies of vitamin C* and rheumatic infections has been reviewed by J. F. Rinehart (Ann. Int. Med. 9: 586 (Nov.) 1935). Guinea-pigs which were fed diets adequate in every respect except in vitamin C developed degenerative changes in the heart valves and lesions in the heart muscle which were similar to those of early acute rheumatic fever. When these animals were given injections of pathogenic organisms, additional degenerative and proliferative lesions occurred on the heart valves beneath the endocardium resembling the pathology of rheumatic fever. One of the common symptoms of vitamin C deficiency in the guinea-pig was pain, tenderness and swelling of the joints. In most patients, both rheumatic fever and scurvy produce a tendency to hemorrhage and an alteration in connective tissue substances. In a review of the epidemiological factors which were common to both diseases, it was noted that malnutrition was frequently seen in both types of patients, the geographic distribution and the seasonal incidence of the 2 diseases were somewhat similar, and both conditions occurred most frequently in patients of the lower economic levels and in childhood, especially in children living in urban centers. It was thought that the existence of latent scurvy was more widespread than was generally believed, especially during the years of economic depression when diets were inadequate. The author does not exclude the possibility of a super-

imposed infection as the true cause of rheumatic fever, but the vitamin C deficiency seemed to aid in increasing the susceptibility of the patient to these other types of disease.

The possibility that the *type of food intake* had some influence on the occurrence of rheumatic fever led to a study of the diets of children with the disease in comparison with those of normal children by E. C. Warner and F. G. Winton (Quart. J. Med. 4: 227 (July) 1935). The incomes of families in which there were children with rheumatic fever were found to average slightly higher than the incomes of the control families. No signs of undernutrition or lack of normal physical development were discovered in the rheumatic families as a rule, and the total caloric intake of food of rheumatic children and their families was sufficient and as great or greater than that of the control groups. The total protein intake of rheumatic families was generally higher than that of control families, but the proportion of animal protein consumed by the children of both groups was thought to be insufficient. Rheumatic children consumed an amount of fat somewhat greater than normal children, but the intake of fresh dairy products such as milk and butter was considerably lower than the average recommended for children. Carbohydrates, potatoes and fresh fruits were taken in greater amounts by rheumatic families than by normal groups. There did not seem to be any deficiency of vitamins in the diets of rheumatic fever patients. It was concluded that no single factor of diet could be assigned as a factor leading to the rheumatic infection, but the intake of animal protein and of dairy products was low and the consumption of potatoes and other carbohydrates by rheumatic children was high in comparison with the nonrheumatic group.



**Pathology.**—The incidence of *rheumatic pleurisy* is more common than the clinical evidence of the disease would indicate, according to the studies of S. Starr and P. Parrish (Am. J. Dis. Child. 50:1187 (Nov.) 1935). With the aid of x-ray pictures taken with the patients in anteriorposterior and oblique positions, interlobar pleurisy was found to occur in 43.6 per cent. of a group of 85 patients with rheumatic fever, in 13.5 per cent. of a group of 36 patients with chorea, and in only 9 percent. of a group of normal children. The thoracic and abdominal pain noted in association with pericarditis was thought to be due in some instances to pleurisy which either preceded or occurred after the onset of the pericarditis. In a few patients observed by the authors, rheumatic pleurisy had been mistaken for pneumonia because only anteriorposterior x-ray pictures had been taken, but the lesion could be demonstrated to be entirely interlobar by oblique or lateral views of the chest. In 1 instance a patient had the signs and symptoms of pleural involvement but no evidence of it could be found on x-ray examination.

*Skin lesions* of an *annular* type have been noted in 6 rheumatic patients by A. F. Abt (Am. J. M. Sc. 190:824 (Dec.) 1935). These lesions occurred in semicircles or in rings, most numerous on the trunk and rarely on the extremities. They were pale or bluish-red in color, macular in shape and tended to disappear without scaling. The presence of such lesions was usually accompanied by the occurrence of a rheumatic infection. This type of erythema annulare rheumaticum was thought to be specific of rheumatic fever infections and to occur more frequently than subcutaneous nodules. Some authors have found the lesions in two-thirds of all children with rheumatic endocarditis.

**Diagnosis.**—Certain types of *mid-diastolic murmurs* frequently interpreted to be mitral stenosis are not necessarily typical of that cardiac lesion, according to E. F. Bland, P. D. White and T. D. Jones (Am. Heart J. 10:995 (Dec.) 1935). In a series of 100 patients who died with mitral stenosis, 68 had clinical evidence of the disease—a rumbling diastolic murmur heard at the apex of the heart. Thirty patients of this same group had diastolic thrills. At autopsy only 21 were found to have an anatomic stenosis of the mitral valve, and in 19 additional cases there were wrinkling and deformity of the valve leaflet, but no real stenosis. The remaining number of patients had no deformity or a very small amount of thickening at the free edges of the valves.

Other common findings at autopsy which may have produced the type of murmur were cardiac enlargement with hypertrophy and dilatation, flabby muscular walls of the ventricles and histologic evidence of rheumatic myocarditis. Children who had had recent rheumatic infections had cardiac dilatation and fresh rheumatic lesions in the heart, but the minimum of 2 years or more was usually found to have elapsed before a true deformity of the valves and stenosis of the orifice occurred.

It was believed that the typical mid-diastolic or presystolic rumbling murmur in early cases of rheumatic fever probably indicated active infection and possibly cardiac dilatation. In other patients who had had rheumatic infection for 2 years or more and had no evidence of recent active infection, these typical murmurs probably represented true mitral stenosis. Murmurs occurring after recent infection, which suggest mitral stenosis, often tended to disappear as the condition of the myocardium improved and ventricular dilatation subsided.

Among the tests indicating activity of rheumatic infection is the behavior of the *eosinophils*. In a study of 7 patients, G. Friedman and E. Holz (J. Lab. and Clin. Med. 21:225 (Dec.) 1935) found that the eosinophils characteristically (1) disappeared from circulation during acute stages of polyarthritides and carditis; (2) reappeared during recovery; (3) were sometimes increased in number in cases of continued activity; (4) increased temporarily or were absent during minor exacerbations of rheumatic heart disease. It was concluded generally that an absence or a diminished number of eosinophils for a long period of time indicated intense activity of the infection, and that the recurrence of the cells or continued eosinophilia was usually associated with convalescence.

Within recent years the *sedimentation rate of red blood cells* has been employed frequently in the determination of the course and prognosis of rheumatic fever. A favorable report of the value of this test has come from W. W. Payne and B. Schlesinger (Arch. Dis. Childhood 10:403 (Dec.) 1935). They employed it in the examination of 140 children with no evidence of activity of the disease and found the sedimentation rate normal in all but 3 instances. In 89 patients with active rheumatic fever the sedimentation rate followed the general clinical course in most instances. In chorea patients the sedimentation rates were usually normal. Acute infections such as influenza, tonsillitis, and anemia also caused increased rates. The test was thought to be of special value in the detection of subacute rheumatism and in determining the prognosis of the disease and of certain related manifestations such as rheumatic nodules.

In a comparison of various laboratory tests of the activity of a rheumatic infection, J. L. Rogatz (J. Pediat. 8:184 (Feb.) 1936) concluded that after the

temperature and pulse rate of such patients had returned to normal, the immature polymorphonuclear leukocytes disappeared slowly from the blood and last of all the sedimentation rate returned to normal. A study of the Schilling counts and sedimentation rates of 20 children with rheumatic manifestations and of 25 normal children indicated that the *sedimentation rate* was the most accurate test of minimal activity of the infection and this procedure should be used to determine the length of time a rheumatic patient should remain in bed.

**Treatment.**—The influence of the *removal of tonsils* on the manifestations of rheumatic fever has been studied for several years by A. D. Kaiser (J. Lab. and Clin. Med. 21:609 (Mar.) 1936). From histories obtained from the families of 20,000 tonsillectomized children and from families of 28,000 unoperated children, it was found that initial attacks of joint pains and carditis were more frequent in the untreated group, and the incidence of chorea was about the same in the 2 groups. In a series of 439 rheumatic children observed over a period of 5 years, the initial attacks and recurrences were more frequent in children with tonsils than in operated children. A series of 2200 children with tonsils removed were compared with a group of 2200 whose tonsils were not removed. After a period of 10 years, the statistics indicated that the removal of tonsils was followed by a decrease in the incidence of attacks of joint pains and postchorea carditis, but did not seem to have any effect on the incidence of chorea itself or on the development of postarthritic carditis. Tonsillectomy seemed to have no beneficial action in reducing the number of recurrences of rheumatic attacks but the carditis in such children was apparently less severe, and the mortality due to rheumatic fever was

reduced to half of that of a control, untreated group.

**Human convalescent serum** was employed in the treatment of 4 patients with manifestations of rheumatic fever by B. H. Archer (Arch. Pediat. 53:87 (Feb.) 1936). Two patients with chorea received the serum intramuscularly in doses of 8 c.c. and intrathecally in doses of 5 c.c. Patients with joint symptoms and carditis received intramuscular injections only. Clinical improvement seemed to follow the treatment.

**Fever**, induced in patients by radiation, has proved effective in the treatment of 7 children with subacute rheumatic carditis and 1 with severe carditis, according to a report by L. P. Sutton and K. G. Dodge (J. Lab. and Clin. Med. 21:619 (Mar.) 1936). Treatment was given for 8 to 17 days and at the end of this period of time the heart rate was reduced, gallop rhythms disappeared, and in some children the murmurs were no longer heard.

The addition of **magnesium oxide** to **acetylsalicylic acid** in the prolonged treatment of children with symptoms of rheumatic fever was recommended by A. D. Kaiser (J. Pediat. 8:41 (Jan.) 1936). Doses of 10 to 15 grains (0.65 to 1.0 Gm.) of the aspirin were given with an equal amount of magnesium oxide daily for a period of 6 to 12 months. The children were divided into groups of those who had joint pains only, those with cardiac manifestations in addition to their joint pains and those with chorea only. Each group was compared to an untreated control series of the same age distribution and suffering from similar symptoms of the disease. During the period of observation, children with joint pains only and those with chorea who were treated with acetylsalicylic acid and magnesium oxide seemed to do much better than the control series. Very little difference in the course of

the illness was noted in the group of children with cardiac involvement.

**CHOREA**.—In an analysis of the influence of chorea on the development of heart disease, T. D. Jones and E. F. Bland (J. A. M. A. 105:571 (Aug. 24, 1935) stated that valvular disease was relatively rare in children who had had uncomplicated chorea, and less cardiac damage seemed to result from chorea combined with joint pains than from joint pains alone. They found that 50 per cent. of a total of 1000 patients with some form of rheumatic infection had had chorea. Of this number of chorea patients 28 per cent. had had chorea alone and in 72 per cent. the disease occurred together with some other manifestation of rheumatic fever. These observations covered a period of 8 years. Heart disease was found to develop in only 3 per cent. of the group of chorea patients as compared with an incidence of heart disease of 73 per cent. in the group who had had chorea with some other manifestation of rheumatic fever. Patients who had chorea followed by joint pains developed heart disease in much greater frequency than those who had these manifestations of rheumatic fever in reverse order. The death rates were much greater among patients with joint pains only (32 per cent.) than in patients with joint pains and chorea (14 per cent.) or in patients with chorea only (0.7 per cent.).

*Mental changes* occurring in association with chorea have been noted in 30 patients by E. Lesné, C. Launay and P. Guillain (Rev. franç. de pédiat. 11:583, 1935). In 60 per cent. of the group, mental disturbances disappeared completely within a few weeks after the onset of the disease, but in the remaining 40 per cent. of cases, changes in behavior and emotional instability remained for a considerable length of time. It was the authors' opinion that the ma-

jority of chorea patients develop some mental disturbances shortly after the onset of the illness and a few children have exacerbations of the behavior symptoms without any recurrence of the choreiform movements. It was thought that pathologic changes in the brain substance occurred in chorea which caused the mental disturbances.

**Treatment.**—Favorable results were obtained with **artificial fever therapy** in 13 cases of chorea reported by C. H. Barnacle, J. R. Ewalt and F. G. Ebaugh (J. A. M. A. 106:2046 (June 13) 1936). The fever was induced by the Kettering hypertherm. The first 8 patients received treatment for 2½ hours at intervals of 3 to 6 days, the temperatures ranging from 103° to 106° F. (39.4° to 41.1° C.), and the last 5 patients received treatment daily. Daily treatment seemed to give better results than treatment at intervals of longer duration. All of the patients recovered after an average of 34 days when the treatment was given intermittently and after 9 days of the daily treatment. Advanced endocarditis seemed to be no contraindication to the treatment.

**ENDOCARDITIS.**—An instance of acute mitral endocarditis occurring in a premature infant was observed by A. Plaut and G. Sharnoff (Arch. Path. 20: 582 (Oct.) 1935). The infant lived but an hour and at autopsy a small lesion resembling a hematoma the size of a pin-head was noted on the mitral valve. On microscopic examination, this vegetation was found to consist of a fine fibrous network containing many polymorphonuclear leukocytes with erosion of the endothelial lining of the valve and some swelling of the tissue beneath. There was no evidence of the cause of this endocarditis nor were any bacteria found in the microscopic sections. In a review of the literature, the authors found only 1 other such case reported with

autopsy findings indicative of true inflammatory process. Several other cases have been reported with some chronic tissue changes not necessarily due to fetal endocarditis.

**ELECTROCARDIOGRAPHY IN NORMAL CHILDREN.**—Electrocardiograms were taken of 167 healthy children by C. T. Burnett and E. L. Taylor (Am. Heart J. 11:185 (Feb.) 1936) in order to determine the normal variations. The ages of the children ranged from 1 month to 12 years and the records were obtained on repeated occasions from the individual patients, the average number being 7.6. In summarizing their results, the authors found that the P-waves varied in amplitude more than in adults, although an average of the height of the wave in all 3 leads was not much different from that of the adult readings. Notched and diphasic forms occurred frequently in electrocardiograms of children. Large Q-waves occurred frequently in healthy children, more frequently in boys than in girls and there was a tendency for this wave to decrease in amplitude with advancing age. R-waves varied greatly in amplitude, much more so than in adult records. Slurring occurred in this wave in 35.8 per cent. of the tracings and notching in 4.38 per cent. The amplitude of the S-waves decreased with advancing age of the patients. High T-waves in the first 2 leads was a frequent finding and inversion, which occurred only in the third lead, was present in 18.9 per cent. of the tracings. P—R and Q—S intervals were shorter in time than in adults and tended to increase with advancing age of the children. Sinus arrhythmia was noted in 21.8 per cent. of the records, most frequently in children in their tenth and eleventh years. Right axis deviation was most frequently noted in infants less than 4 months of

age and disappeared rapidly within the next few months. Left axis deviation was noted in a few instances in average healthy children. The authors believed

that these observations indicated that the variability of electrocardiograms of children was much greater than that observed in the tracings of normal adults.

## INFANT FEEDING

By WALDO E. NELSON, A.B., A.M., M.D.

**BREAST MILK.**—A method for the *preservation* of breast milk is described by L. A. Scheuer and J. E. Duncan (Am. J. Dis. Child. 51:249 (Feb.) 1936). Their description of the technic is as follows:

Seven ounces (210 c.c.) of unpasteurized breast milk with  $\frac{1}{2}$  ounce (15 c.c.) of sterile water was placed in each of a number of ordinary 8 ounce (240 c.c.) formula bottles. Sterile corks were then placed in the bottles but were not pushed down tightly, as they would blow out when the milk was heated. Over each of the corks were placed 6 layers of sterile gauze, a large piece of cotton and finally a piece of paper. This covering was secured by means of a large rubber band. The bottles were then placed in a bottle rack of 8 sections. The rack was placed in the top of a double-boiler in cold water which reached to the level of the milk in the bottles. The water was maintained at a temperature of 175° F. for 30 minutes. The bottles were then kept for 24 hours at room temperature. At the end of this time the process was repeated and again at the end of 48 hours. Following this third heating, the corks were tightened in the bottles, the coverings of the corks were removed and the corks were sealed in paraffin. Finally the bottles were stored in the refrigerator at a temperature of 38° to 52° F.

The clinical experience of the authors with milk preserved in this manner extends over a period of 2 years. Repeated bacteriologic examinations of the specially pasteurized breast milk showed that it remained sterile if it were properly refrigerated. Chemical analysis at the end of the second year showed similar values for the specially pasteurized milk and for fresh breast milk. The same fecal flora were found in the stools of infants fed this specially pasteurized

breast milk as in infants fed fresh breast milk. For the feeding of premature and malnourished infants it was found to be a satisfactory substitute for fresh breast milk.

An excellent review of infant feeding is presented by G. F. Powers (J. A. M. A. 105:753 (Sept. 7) 1935). For the information which it contains, as well as for its wealth of common sense, this article is worth reading in its entirety.

In regard to the *quantitative intake* of infants, it is suggested that the number of calories, except in the case of the sick, feeble, or premature infant, can be safely left to the baby when the supply of milk is adequate. In regard to the *qualitative aspect* of the various components of the modified milk formula, it is recommended that 10 to 20 per cent. of the calories should be proteins, not more than 35 per cent. in fat, and the remainder, at least 50 per cent., in carbohydrates. One means of arriving at a satisfactory mixture is by adding 10 per cent. sugar to one-half skim milk. According to the author, this mixture usually requires no added water and is not too concentrated for the average infant.

Attention is called to the part that psychologic factors play in disturbances in artificial feeding: "The problems are sequelæ in part—possibly in large measure—of a strict, dogmatic attitude in the application of the advances in the science of nutrition to the practice of infant feeding; pediatricians and mothers alike have the 'itch' for regulation grow-

ing out of aspiration for perfection in dietary régime and habit training and as a direct result of the propaganda for weighing and measuring—in short, for standardization.”

“The most important aspect of the emotional problem in infant feeding is recognition that the problem exists and to a large degree may be prevented if the physician has insight and understanding of the personality of the mother and takes pains to prepare her to meet situations that are bound to occur in every case. The physician may need the assistance of a psychologist or a psychiatrist or both but the burden of prevention is wholly that of the physician who guides the feeding. Here, if anywhere, ‘An ounce of prevention is worth a pound of cure’. But prevention means understanding, insight, tact and patience.”

**ACID MILK.**—K. B. Rothery (J. Pediat. 7, 60 (July) 1935) has shown that lactic acid milk has a bactericidal action. Several different strengths of lactic acid milk were contaminated with various organisms. It was found that milk containing 0.66 per cent. or more of lactic acid is bactericidal and will prevent contamination of the milk with dysentery and typhoid organisms. Infants will drink milk containing 0.75 per cent. lactic acid. The use of bactericidal or antiseptic milk is recommended to prevent milk-borne infections. It is also suggested that this bactericidal action is helpful in reducing the growth of bacteria in the upper intestines during diarrheal infections.

The author's instructions for preparing lactic acid evaporated milk are as follows:

The contents of a 13-ounce can of unsweetened evaporated milk are poured into a quart bottle, previously scalded with boiling water. The empty can is then nearly filled with boiling water in which is dissolved 1 teaspoonful of lactic acid (U. S. P.) and 3 level table-

spoonfuls of cane sugar. As soon as this solution is cold, it is mixed slowly, being stirred constantly, with the unsweetened evaporated milk. In order for the lactic acid to exert a bactericidal effect, it is recommended that the mixture be kept for 6 hours, preferably, though not necessarily, in a cold place before being fed in required amounts to the infant. In order to prevent curdling, the mixture should not be repasteurized or boiled after it has been mixed.

In conjunction with the investigations by Rothery, the clinical experience of L. A. Scheuer (*Ibid.* 7:468 (Oct.) 1935) in the use of lactic acid milk for the *prevention of summer diarrhea* is of particular interest. This report is from the New York Foundling Hospital. In each year from 1910 to 1930, inclusive, there were a variable number of cases of summer diarrhea with a high mortality rate. This occurred notwithstanding an adequate, clean milk supply with a low bacterial count. From 1931 to 1934, inclusive, 403 malnourished infants under 6 months of age were fed a powdered, whole lactic acid milk mixture, containing a total carbohydrate content of 7 per cent. and 0.3 per cent. lactic acid. Each infant received less than 50 calories per pound of body weight per day. In this 4 year period there were no instances of summer diarrhea among the 403 infants who were fed this type of lactic acid milk mixture.

Satisfactory experience in the use of buffered lactic acid evaporated milk for the feeding of infants, particularly in the case of premature and congenitally debilitated infants, is reported by F. S. Smyth and S. Hurwitz (J. A. M. A. 105:789 (Sept. 7) 1935). The buffer solution consists of 15 c.c. ( $\frac{1}{2}$  ounce) of lactic acid, 20 c.c. (5 drams) of 10 per cent. solution of sodium hydroxide and water to a total 500 c.c. (1 pint). This is made up as a stock solution. Equal parts of this mixture and of evaporated milk, to which is added 10 per

cent. Karo syrup, is used as the feeding formula. This formula has a caloric value of 110 calories per 100 c.c. The pH value is 4.2, approximately the hydrogen ion concentration of gastric juice at the time of optimum digestion in an infant being fed cow's milk.

It is claimed that this buffer formula maintains a more adequate acidity than that of the usual lactic acid formula. In addition to having a smaller curd than nonacid milk, it is claimed that it tends to inhibit the growth of *B. coli* in the upper intestinal tract and in the stomach. According to the authors' experience, this milk is well tolerated in the first weeks of life, and infants fed on this mixture have a lower initial loss of weight, regain their birth weight more rapidly, and have a lesser degree of icterus neonatorum. It is recommended in particular for *prematures* and for *congenitally debilitated infants*.

**CEREALS.**—M. L. Blatt and I. E. Schapiro (Am. J. Dis. Child. 50:324 (Aug.) 1935) have studied the influence of the special cereal mixture, described by Tisdall, Drake and Brown on a group of institutionalized infants, ranging in age from birth to 3 years. This cereal mixture (Meade's Cereal) is rich in vitamins and mineral elements. The children were divided into 2 groups as nearly equal in age, sex, race, social status, body build and management as selection would permit. Both groups received the usual diets for their respective ages with the exception that one group received this special cereal mixture, while the control group received the commonly used cereals. Their observations showed that the group fed the special cereal mixture exceeded the control group in weight, total length, stem length, and circumference of the chest and head. From the records of dentition, it was shown that those fed the special cereal mixture had an earlier eruption

of teeth. The hemoglobin values were higher in that group receiving the special cereal mixture. No relationship could be shown between the constitutional index and the incidence of infection.

**ALLERGY.**—According to B. Ratner (J. A. M. A. 105:934 (Sept. 21) 1935), hypersensitiveness or allergy to milk is of more frequent occurrence than is generally realized. The soluble whey proteins of raw cow's milk, lactalbumin and lactoglobulin, are most often responsible for the allergic manifestations; casein plays a negligible rôle. Ratner believes that allergy is acquired and not inherited and thus is controllable by preventive measures. The recommended treatment is elimination of raw milk from the diet, replacement of it by denatured milk, and the establishment of tolerance by the slow and gradual introduction of raw milk. Ratner summarizes the treatment and prevention of milk allergy as follows:

**Prevention.**—1. By advocating the taking of moderate amounts of milk during the period of pregnancy and the avoidance of excessive indulgence in raw milk during the latter months of gestation, so as to avoid the possibility of inducing congenital sensitization. If milk is desired in more than moderate amounts, a portion should be in the form of denatured milk.

2. By avoiding isolated feedings of raw cow's milk to the breast-fed infant during the newborn period.

3. By giving no raw cow's milk during convalescence from disease and during and after gastrointestinal disturbances.

4. By refraining from the use of excessive and exclusive milk diets.

5. By eliminating the use of injections of milk for nonspecific therapy.

**Treatment.**—1. The elimination of all raw milk from the diet, including milk used in the preparation of foods.

2. The substitution of a milk subjected to intense and prolonged heat in a liquid state.

3. The gradual immunization of the patient by the oral administration of minute amounts of raw milk, with the

continued use of the denatured milk throughout the entire period.

4. The final substitution of adequate amounts of raw milk, which must then be taken continuously in moderate amounts.

## INFANT MORTALITY

By WALDO E. NELSON, A.B., A.M., M.D.

In recent studies, Bakwin and Bakwin showed that infants who had medical supervision during their first weeks of life, had a greater increase in body weight and total body length in contrast to a group of nonsupervised infants. Both the rates of illness and of mortality were higher in the undergrown infants.

In Clifford's efforts directed toward the reduction of neonatal mortality, he stressed the importance of delaying birth, if possible, until the fetus approaches the average birth weight. This is extremely important, since 50 per cent. of neonatal deaths occur in premature infants. He has developed an x-ray technic for the determination of the occipitofrontal diameter of the fetal head. From this measurement it is possible to determine the relative age and weight of the infant. In regard to the effect of the method of delivery and of morphine administration to the mother upon premature mortality, Clifford observed that the lowest mortality occurred when the infant was delivered by application of low forceps after a wide episiotomy had been made. Administration of morphine to the mother within 4 hours of birth greatly increased the mortality rate.

The provisional infant mortality rate for 86 large cities in the United States in 1935 was 49 per 1000 live births (Pub. Health Rep. 51:112 (Jan. 31) 1936). In 1934, the rate was 55 for this same group of cities. With the

rapid decline in the birth rate, the need for efforts directed toward the reduction of infant mortality is becoming increasingly important. While there has been marked reduction in the mortality rate after the first month of life, there has been little change in the mortality rate during the newborn period for the past 30 years or so. F. L. Adair and E. L. Potter (Am. J. Pub. Health 26:281 (Mar.) 1936) point out that there has also been practically no change for the rate of stillbirths since vital statistics on this subject have been collected. They emphasize that attempts to lower the neonatal death rate cannot be made without also attempting to lower the stillbirth rate, since deaths in both groups are frequently due to the same fundamental causes. The points enumerated for the prevention of antenatal, intranatal and neonatal deaths are: Better prenatal hygiene, immediate and appropriate treatment of toxemia, correction of malpresentation, appropriate treatment of cases of contracted pelvis, prevention of onset of labor until as near term as possible, more skilled obstetric technic and better immediate care of the newborn child, especially those born prematurely.

With so much emphasis focused upon the neonatal period, there may be a tendency to neglect or at least to be satisfied with the progress which has been made in the reduction of mortality after the first month of life. The great



need in this respect is education of the masses in ordinary hygienic measures. This includes such factors as a non-contaminated food supply which is nutritionally adequate, isolation of all infectious diseases, no matter how trivial, and adequate rest. Education of this nature is best done individually and should be part of the service of the general practitioner or pediatrician and the public health nurse. The value of a systematic campaign is illustrated by the report of the Public Health Federation of Cincinnati for August, 1936. In a selected area of the congested portion of the city, adequate home supervision by a group of graduate nurses was pro-

vided during the summer months for 2 consecutive years. Each home in which there was an infant under 2 years of age was visited at least once a week. Any child under observation who had evidence of illness was visited at more frequent intervals, and when necessary, was hospitalized. The two factors which seemed most important in this program were: home instruction of the mothers in proper care and feeding of the infants and the early recognition and treatment of enteritis. Not only was the mortality rate from enteritis decreased in this area as compared with previous years, but the rate was lower than that of the adjacent and corresponding sections of the city.

## ACUTE INFECTIOUS DISEASES

By ROBERT A. LYON, A.B., A.M., M.D.

The application of strict *quarantine* rules reduces the availability of a pediatric hospital for the admission of patients for many days throughout a year. The rigidity with which such regulations were followed in hospitals in different localities was investigated by C. Kereszturi, D. Hauptman, W. H. Park and F. Bartlett (J. Pediat. 8: 166 (Feb.) 1936) and found to vary considerably. As an experiment, they replaced quarantine and aseptic technic in their hospital for a period of 3 years with the administration of specific convalescent serum for one-half of the group of children exposed to a contagious disease and left untreated the other half of the group to serve as a control. Their hospital had space for 63 beds which were separated from each other by glass partitions. In the summary of their investigation, they reported that no secondary cases of German measles, whooping cough or scarlet fever occurred during the 3-year period and

the incidence of cross infections of measles and mumps was reduced, but the spread of chickenpox was not affected by the use of the serum. Only 47 per cent. of 1717 children admitted to the hospital were susceptible to the contagious diseases to which they were exposed and 4.6 per cent. of this number contracted a contagious disease from exposure in the hospital. It was concluded that the replacement of quarantine regulations by other measures did not seem to increase the rate of cross infections in the children's wards. The disadvantages of the quarantine rules were thought to be greater than the benefits of their use. During the time that the quarantine rules were disregarded, the hospital became available for 462 days more than under the previous régime of adherence to the regulations and this allowed additional facilities for the care of patients, training of the staff, and increased the monetary income.

## JUVENILE DELINQUENCY

By ROBERT A. LYON, A.B., A.M., M.D.

The relationship of *mental retardation* to *juvenile delinquency* has been reviewed recently by E. T. Glueck (Ment. Hyg. 19: 549 (Oct.) 1935). In a series of 1000 male juvenile delinquents appearing before the Boston Juvenile Court, about 30 per cent. were feeble-minded with intelligence quotients of 70 or below. These figures were comparable to those obtained from a study of 3600 children in which mental retardation was found more frequently in delinquents than in normal children. A comparison of the patients who were low in mentality and those who were normal or higher in mentality indicated that the delinquent children with low mental levels had been arrested as frequently, at as early ages, and as soon after the first delinquent act as had more intelligent children. These statistics indicated that previous statements were incorrect, which implied that children of low intelligence were more prominent in such studies of delinquency because they had been apprehended more readily.

Children of low intelligence were found to come from families which were lower than average in mental development, and the parents of these patients were found to have married at an early age and had had less schooling than the parents of more intelligent children of the delinquent groups. The parents of the juvenile delinquents of low intelligence were more frequently employed in unskilled types of labor than the parents of the other children; poverty was a greater factor among them; their homes were more crowded and less attractive; the families were larger; there was less affection and discipline in the families; broken homes were more frequent, and their homes were more often located in noisy neigh-

borhoods in which crime was frequent. In regard to the boys themselves, it was found that those with the lower intelligence were susceptible to suggestion, had poor emotional control, but had a less abnormal ideation than the boys with normal mentality. Their physical development was not as good and, of course, they had not done as well in school as the children in higher intelligence levels. Children of the lower intelligence levels had belonged to fewer clubs or organizations and had entered the skilled trades in smaller numbers than had the more intelligent boys. The 2 groups resembled each other in the size of their families and in incidence of foreign born parents. The delinquents of each group were apprehended at about the same age, the average time of the first offence being about 9 years. The homes of both types of delinquents were inadequate, disturbances of family life and the lack of disciplinary measures were common in both groups and social agencies had been compelled to give relief to both groups in about the same proportion. Therefore, the environment of the children in the 2 groups had been somewhat the same and it was the opinion of the author that, although mental deficiency could not be assigned as the cause of delinquency, it certainly was a complicating factor, and when it occurred in an individual placed in unfavorable surroundings, it would tend to lower his resistance to asocial behavior.

*Treatment* seemed to depend considerably on the type of delinquent child, and in this respect the school had considerable influence in the determination of his behavior. **Institutionalization** was necessary for certain delinquents of low intelligence levels, especially for those who had such an unstable emotional

or psychopathic make-up that they might be dangerous to society. About one-third of the group of mentally defective delinquents had been referred to institutions and only about one-tenth of the number of delinquents of higher intelligence had seemed to require this type of treatment. For the remainder of the children, the best treatment seemed to be **close supervision**. The detection of the onset of delinquent behavior is necessary so that early observation and treatment may be instituted. The schools should be equipped to detect the children with mental deficiency in the early grades, to arrange for specialized types of instruction leading to a careful selection and training for their vocational life, and should try to prevent the formation of antisocial habits. The training, however, should not be limited to the school, but should include supervision of the child at home and the planning for his leisure time so that he will be constantly occupied in a favorable environment.

The problem of the defective delinquent has been discussed recently by M. Harrington (*Ibid.* 19:429 (July) 1935). Environmental factors which are in a large part responsible for delinquent acts of the mental defective seemed to arise in the home, neighborhood, school, and conditions of employment. The possibility of influencing the conditions of any of these places except the schools, seemed very remote unless by some widespread social and economic changes. Children in rural districts are less affected by environment, especially of the neighborhood and conditions of employment, than are the children and young adults of the city, because on the farm, the opportunities for work are more plentiful, the type of work is more adapted to low intelligence levels, and the neighborhoods are not so apt to contain influences which would lead such an individual into crime. The schools must

assume the burden of responsibility for preventing delinquent acts by the defective children. By means of ungraded classes and special instruction, the defective child has been able to profit from his education, but Harrington believes that the mentally retarded child should also have (1) more adequate **recreational facilities** to help his physical and mental development and to eliminate the possibility of association with other persons with criminal tendencies; (2) **psychiatric service** to take care of special problems; and (3) **vocational guidance** to train the defective and plan for employment or some profitable occupation.

Another study of the intelligence of a group of young adult delinquents was made by G. E. Hill (*J. Juvenile Research* 20:20 (Jan.) 1936). The *Army Alpha test* was given to 1285 inmates of an institution ranging in age between 16 and 26 years. Very few were feeble-minded and the average scores were in the dull, normal levels which placed the majority of the delinquents above the mental levels of the men drafted for the army. No definite relationship between the intelligence and the age of the patient at time of commitment to the institution could be established, nor was there any relationship between intelligence and the type of crime committed. The white boys were more intelligent than the negroes and first offenders were less intelligent, as a rule, than those who had committed several delinquent acts. Boys with low intelligence had been retarded in their advancement in school and apparently there had been many handicaps to their success and achievements in their school life. A proper adjustment of the child to his surroundings and to his life work is very necessary, and the author believes that the school could do a great deal in adjusting the program of such a child so that he

would be more satisfied and better trained to take his place in the community.

The *hearing ability* of 480 boys between the ages of 8 and 17 who had been committed to an institution because of some behavior problem, was tested by M. Molitch (*Ibid.* 20:15 (Jan.) 1936). The intelligence levels of one-fourth of the group were subnormal and about one-half of the group were in the lower normal ranges. Impairment

of hearing was most frequently encountered in children with other physical defects, such as chronic otitis media, congenital syphilis, endocrine disturbances, and in children who could not read well. About one-half of the number of children with slight impairment of hearing were unaware that such a condition existed. Defective hearing was thought to have some influence on the behavior and adjustment of the children.

## MALNUTRITION IN CHILDREN

By WALDO E. NELSON, A.B., M.D.

**GROWTH CHART.**—A chart for the plotting of a graphic record of growth in children from 1 to 19 years of age has been described by L. M. Bayer and H. Gray (*Am. J. Dis. Child.* 50:1408 (Dec.) 1935). Chart I illustrates the set-up of this graph. In this chart the average height and weight of each age is shown by a solid dot, with the age indicated beside it. Each vertical bar represents a variation of height for age of plus or minus twice the standard deviation, or the range which is expected by chance to include 96 per cent. of normal children of race and environmental advantages similar to those of the children from whom data for the diagram were derived. The expected deviation of weight for height is shown by the open stream which is delimited by 2 smoothed curves through points representing values of plus or minus twice the standard deviation of weight for children of several statures. The area in the lower right hand corner is set aside for numerical entries.

In plotting, each pair of values for stature and weight is registered as a circle and each pair for stature and bicristal diameter as a cross, with the age expressed in years and months beside them (see Chart II). It should be

noted that the scales for bicristal diameter are graduated unevenly. This is done so that the average bicristal diameter for each age will coincide roughly with the average weight for that age. In the evaluation of the bicristal diameter in relation to stature, if the build is normal, the cross is expected to lie near the circle or not distant by more than one-half the width of the open area, but if, for example, the cross is near the left border of the stream while the circle is near the right (even though both are within the limits of normal values), the weight may be considered too high for the bony build. The authors point out that for very plump children, the bicristal diameter may be used only with reservations as a criterion of build, since, when there is much fat over the bony eminences, this measure has questionable value for the prediction of weight.

**NUTRITIONAL EDEMA.**—The observations of K. Dodd and A. S. Minot (*J. Pediat.* 8:442 (Apr.) 1936) show that generalized edema secondary to nutritional disturbances and unassociated with cardiac or renal disease is fairly common in infancy and childhood. This type of edema is most characteristically associated with malnutrition. The

On the assumption that many of the poorer children in the clinic might have milder degrees of the same nutritional deficiency which had not resulted in manifest edema, Dodd and Minot (*Ibid.* 8:452 (Apr.) 1936) determined the

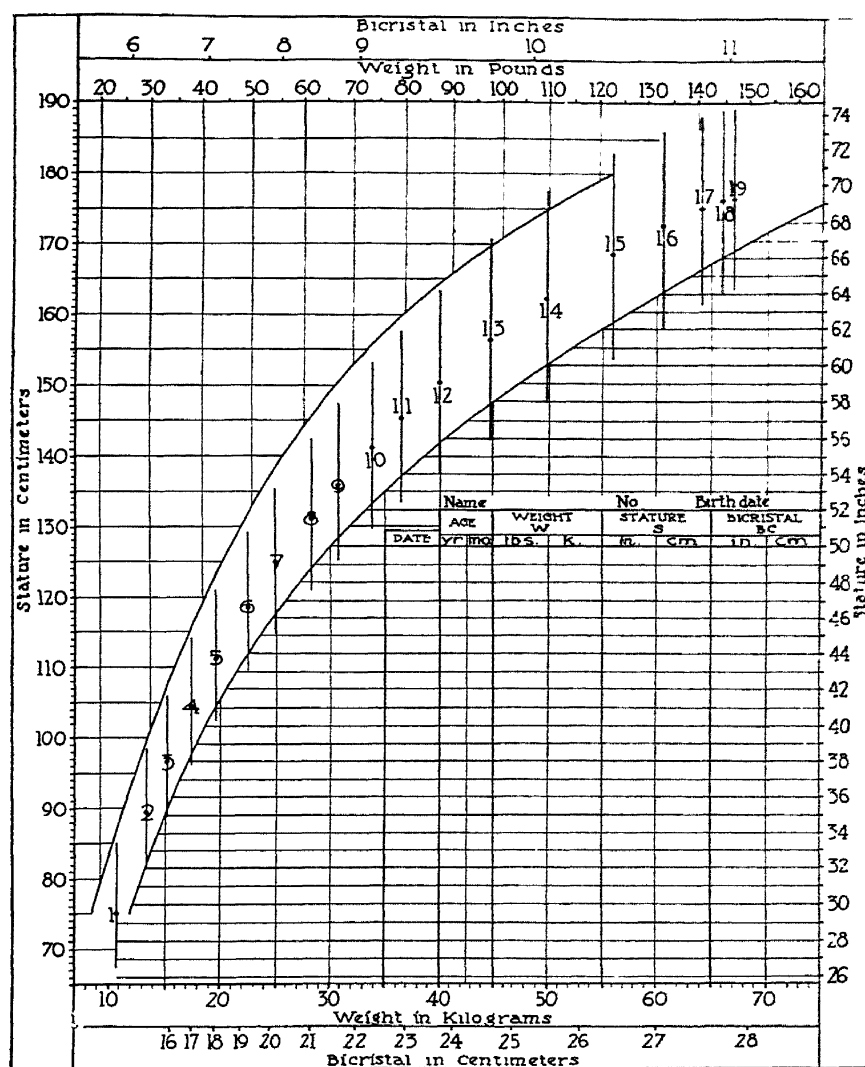


Chart I.—Graph showing range of values for height and weight for boys of from 1 to 19 years. (Bayer and Gray: *Am. J. Dis. Childhood.*)

serum protein level of 500 children in their out patient dispensary. The general level of serum albumin in this group, even in the absence of acute or chronic illness, was somewhat below that of a normal control group. The authors interpret this as evidence of a nutritional disturbance analogous to sub-

clinical vitamin deficiency. A few of these children had edema when first seen. Several of the sick and dehydrated children developed edema following the administration of moderate amounts of

protein is common among the poorer children in the community studied. The diet which is low in total calories and in protein is probably the cause of the deficiency.

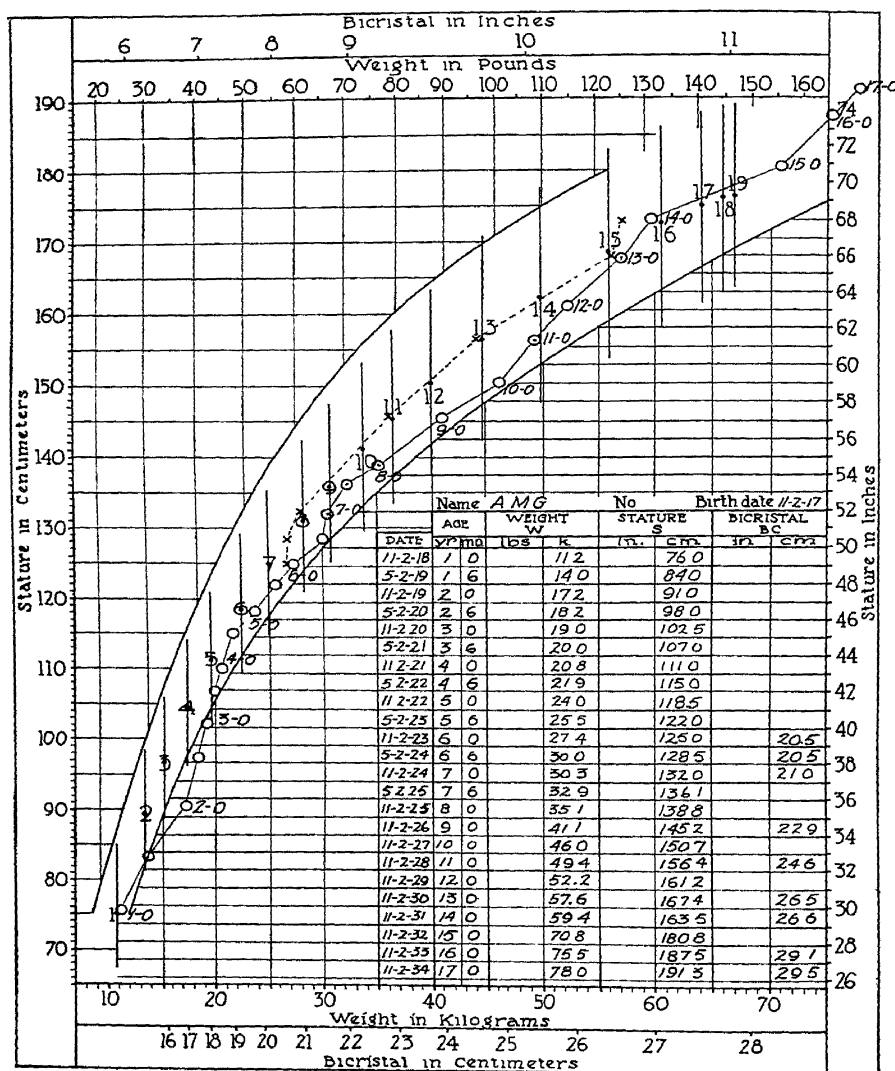


Chart II.—Graph for a very tall, well-nourished boy. The plot for height shows that at age of 2 years the boy was of average stature but since that time he had grown always relatively taller: At age of 7 his height was at level of average boy of 8; at 10, at that for a boy of 12, etc. It remained, however, within the expected variation for his age until time of plotting last circle, when at the age of 17 he was taller than 96 per cent. of boys of 17 and even of 19. Curve for weight shows that boy was somewhat heavy, being definitely overweight between ages of 1½ and 3 years, but that position of circles for weight approached middle of stream in adolescence. Crosses for bicristal diameter show that bony breadth was about that of average throughout period of observation. (Bayer and Gray: Am. J. Dis. Childhood.)

parenteral saline solution. Such children seemed predisposed to the development of edema, especially in the presence of infection. This work indicates that a chronic lowgrade deficiency in serum

**DENTAL CARIES.**—P. Jay (J. Pediat. 8:725 (June) 1936), in summarizing his paper on the problem of dental caries in relation to bacteria and diet states: "It is true that the problem

of dental caries is still unsolved, but certainly the atmosphere is becoming somewhat clarified. We have been a bit sidetracked by the revolutionary contributions made by nutrition. It is becoming quite evident that caries susceptibility is not determined by the structure of the tooth. The rate of caries destruction is very likely influenced by the nature of the tooth, but we have ample evidence to state definitely under favorable environmental conditions, the most resistant teeth become carious and poorly calcified, hypoplastic teeth remain caries-free if conditions favorable to caries production are not present.

"There is considerable evidence that these conditions are reflected in the character of the oral flora. If the lactobacilli are numerous, caries will invariably follow, regardless of the quality of the tooth structure. The conditions which determine the ability of these organisms to survive are evidently not influenced by the calcium, phosphorus, or vitamin content of the diet. A protective diet, so far as caries is concerned, need not even be nutritionally adequate if it is low in sugar. In most cases the oral lactobacilli may be inhibited by the depression of the carbohydrate in the diet, although some individuals who seem to be hereditarily immune to caries, remain free of these organisms regardless of the amount of sugar consumed. We are as yet unaware of the nature of this protective factor except that it has a very striking effect on the welfare of the lactobacilli."

**VITAMIN A.**—A clinical study to determine whether vitamin A has any prophylactic value in the prevention of infection in children has been conducted by I. F. Gittleman and A. S. Wiener (*J. Pediat.* 7:81 (July) 1935). It is generally agreed that gross vitamin A deficiency in animals and human beings is associated with increased

susceptibility to spontaneous infections, which may be evident before other external signs of deficiency make their appearance. In order to test the protective value of vitamin A in a group of children, the authors divided the children of an orphanage into 3 groups. In one group the diet was supplemented with halibut-liver oil and in the second with viosterol. The third group served as a control. There were no significant differences in the incidence of infection in these three groups. The authors concluded that the incidence of infection in children receiving such a régime is, therefore, dependent on factors other than the dietary one investigated.

**VITAMIN A DEFICIENCY.**—In a clinical and anatomic study of avitaminosis A among the Chinese, L. K. Sweet and H. J. K'ang (*Am. J. Dis. Child.* 50:699 (Sept.) 1935) present not only a summary of their own experience, but an excellent review of the literature on vitamin A deficiency. The authors emphasize the fact that, unlike experimental animals on well-controlled diets, these patients were almost always suffering from multiple deficiencies. Many of their patients had well-developed evidence of other deficiency diseases. Thus, it was impossible for them to draw definite conclusions in regard to which of the changes were actually due to the deficiency of the fat soluble A factor and which to associated disturbances. However, since keratomalacia or xerophthalmia was a prominent feature in each of the cases, and since the general symptoms were not those usually associated with other known deficiencies, they were assumed to be due in large part to the lack of vitamin A. The most striking feature of avitaminosis A observed by the authors was the great variability in the pathologic processes and in the symptoms of the disease.

**Etiology.**—The disease is essentially one of early life. Chart III shows the age incidence for their series. Of 64 patients below the age of 5, 30 were less than 1 year of age, and of these 22 were less than 6 months of age. The increased incidence in the second and third decades is explained by the number of soldiers and apprentices seen with the disease. These persons are underpaid, poorly fed and are subjected to long, hard hours of work.

tissues. These changes consist of substitution of keratinized stratified squamous epithelium for normal columnar or nonkeratinized stratified squamous epithelium. Such changes are observed in various parts of the genitourinary tract, the respiratory tract, the alimentary tract, and in the eyes and paraocular glands. Other changes consist of atrophy of glandular organs, emaciation and localized edema of the testes and of the salivary glands. Sterility is a constant

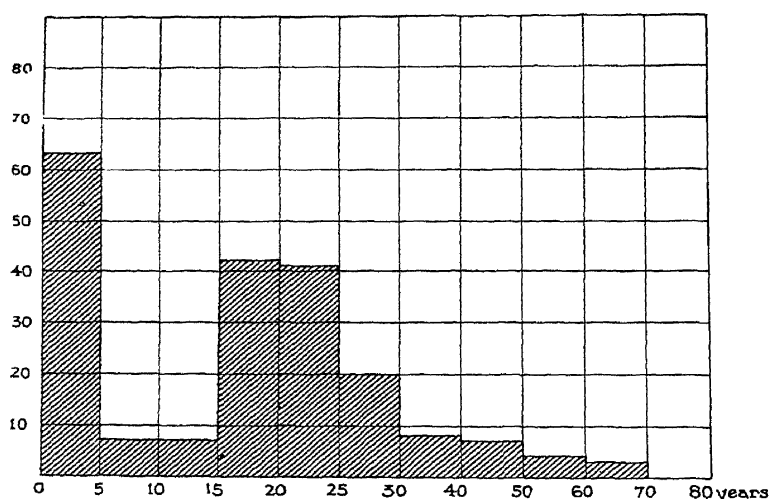


Chart III.—Showing age incidence by 5-year periods in 203 cases of avitaminosis A. (L. K. Sweet and H. J. K'ang. Am. J. Dis. Childhood.)

Sex seemed to be of no significance in the causation of the disease.

Diet is the chief causative factor. If there is an insufficient utilization of vitamin A from any cause whatsoever, over a period of time long enough to deplete the body stores of this factor, the disease becomes manifest. Insufficient vitamin A may be due to: (1) food poor in vitamin A; (2) deficient absorption of vitamin A (digestive disease); (3) increased consumption of vitamin A either during rapid growth or during a severe disease.

**Pathology.**—As shown by the work of Wolbach and Howe, the specific changes in the tissue in vitamin A deficiency affect primarily the epithelial

finding in rats fed diets deficient in vitamin A.

Dryness and scaliness of the skin is a common finding in avitaminosis A. Frazier and Hu were the first to describe a peculiar papular lesion with this disease (see Fig. 1). Microscopically, these lesions consist of small or large papules arising from the pilosebaceous follicles. The openings of the follicles are plugged by masses of cornified epithelium. There is marked hyperplasia of the adjacent epidermis and the interpapillary processes are greatly enlarged. The cutis vera around these follicles shows a chronic and inflammatory reaction and there is also marked atrophy of the sebaceous and sweat glands. In the series ob-



served by Sweet and K'ang, lesions of the eyes were the most frequent finding. These lesions started as keratinization of the cornea and conjunctiva with disappearance of mucous cells. The epithelium of the cornea was hyperplastic and thickened. The corneal stroma showed first edema and then necrosis. This was followed by ulceration and secondary

50 of the cases observed. The onset of this complaint is insidious and may be present for weeks or even months before the appearance of other symptoms. If this symptom is missed, however, there are few or no warning signals in the eyes until the evidence of involvement becomes grossly apparent. At such a time, the patient complains of pain,



Fig. 1.—Papular hyperkeratotic cutaneous lesions associated with avitaminosis A in a youth 17 years old. Three months after appearance of these lesions night blindness and keratomalacia developed. (Courtesy of C. N. Frazier.) (Sweet and K'ang: *Am. J. Dis. Childhood.*)

bacterial infection. Perforation of the corneal ulcer occurred frequently, and in a few cases led to panophthalmitis. If treatment was instituted before perforation took place, the ulceration sometimes healed but there was always a permanent scar.

Of 17 patients who came to autopsy, epithelial metaplasia was present in the larynx or trachea in 8; in the esophagus in 5; and in the urinary system in 3 of the cases.

**Symptomatology.**—The ocular symptoms were the most striking. Hemeralopia or night blindness was present in

lacrimation, redness of the eyes and photophobia. These symptoms usually occur almost simultaneously and the onset is sudden. This is followed by failure of vision, usually associated with a spreading white spot on the cornea. Secondary infection occurs early.

The general symptoms were not so characteristic. Loss of weight was a subjective symptom in only 10 per cent. of the cases. However, nearly all were already poorly nourished before the onset of the symptoms. Loss of appetite was about as common as loss of weight and usually was associated with it. Diar-

rhea, fever and cough were frequent complaints. In many instances diarrhea could be accounted for on the basis of primary dysentery or some other nutritional disturbance. Constipation was a rare complaint. There were several other symptoms less frequently encountered but definitely associated with avitaminosis A, such as headache, hoarseness of the voice, vomiting and general weakness.

Findings on physical examination have been described under pathology.

**Diagnosis.**—In older children and adults, incipient night blindness is the earliest detectable sign. Methods for detecting this have been devised by Birch-Hirschfeld and by Jeans and Zentmire. In young infants, it is practically impossible to detect loss of adaptation to dark. Blakfan and Wolbach suggest examination of the urine, of tracheal secretions or of scrapings from the nose and eye. In any of these the demonstration of cornified epithelial cells is presumptive evidence of avitaminosis A, especially in chronically ill, debilitated infants. However, the finding of abnormal numbers of cornified epithelial cells in the urine is unusual and its absence cannot be relied upon to exclude vitamin deficiency disease. Tracheal secretions are very difficult to secure for examination. The authors have been unable to differentiate by staining between the cells obtained by scraping the buccal mucosa of normal patients and that of patients with advanced keratomalacia. They were able to get more satisfactory evidence of cornified epithelial cells in the nasal scrapings.

In the earliest cases a slight haziness or loss of luster of the conjunctiva was observed. Scrapings made by sweeping a small spatula lightly across the conjunctiva at this time will show keratinizing epithelial cells. When properly stained these scrapings may be shown to contain B. xerosis and pneumococci.

The authors believe that this offers one of the most reliable methods of early diagnosis of avitaminosis A.

The practical use of the *photometer test for dark adaptation* in the detection of vitamin A deficiency is illustrated in the report of P. C. Jeans and Z. Zentmire (J. A. M. A. 106:996 (Mar. 21) 1936). Using this test, the authors found that 26 per cent. of a rural group and 53 per cent. of a village group of Iowa children had evidence of vitamin A deficiency; in an urban group the proportion for the higher economic level was 56 per cent., for the middle level 63 per cent., and for a low economic level 79 per cent. Of the 78 village and rural children who were deficient in vitamin A and who continued under observation, all except three developed normal dark adaptation after a period of vitamin A or carotin ingestion.

**Treatment.**—General measures consist in giving **vitamin A** in adequate dosage. This may be supplied from such foods as liver, milk, butter, eggs, animal fats (except pork fat) and fresh green vegetables. Artificially it may be given as **cod-liver oil**, 15 c.c. ( $\frac{1}{2}$  oz.) or more a day being used. Successful treatment has been reported by the use of **carotin**. When there is evidence of complete lack of absorption of the vitamin from the gastroenteric tract, it may be given parenterally.

#### VITAMIN C DEFICIENCY.—

**Diagnosis.**—An instance of *congenital scurvy* is reported by D. Jackson and E. A. Park (J. Pediat. 7:741 (Dec.) 1935). The baby died when 20 days of age. The clinical diagnosis was acute bilateral otitis media and mastoiditis; acute, severe, nutritional disturbance; acidosis and pyocyanous septicemia. The diagnosis of scurvy was made at the autopsy. When the ribs and femur were sectioned, hemorrhages were observed just beneath the line of ossification and

it was noted that the condition was "much like that seen in scurvy." No subperiosteal hemorrhage was present. X-rays of the bones denuded of soft parts after death were taken but were not pathognomonic of scurvy. This does not seem significant, since the disease must reach considerable development in the skeleton before characteristic changes are discernible in the x-ray picture. The proof of scurvy was established by histologic examination. An interesting observation was that the severity of the lesion at the various cartilage shaft junctions corresponded with the rate of growth. If the rate of growth was slow enough at the end of a bone, the signs of the disease did not appear.

It is important to note that the mother of this infant had a markedly inadequate diet during her pregnancy and was admitted to the hospital 2 weeks postpartum for a hip complaint, which presumably might have been a lesion of scurvy.

X-ray changes in the long bones which make it possible to diagnose scurvy somewhat earlier than previously are described by E. A. Park, H. G. Guild, D. Jackson and M. Bond (*Arch. Dis. Childhood* 10:265 (Aug.) 1935). Their description of the changes at the wrist are as follows:

*Wrists* (Fig. 2).—(The x-ray films were taken with the forearm supinated.) At the wrists the most common early sign of the disease was a defect of the outer corner of the lower end of the radius. In its earliest development it appeared as scarcely more than a fuzziness of the cortex and the slightest rarefaction of the neighboring cancellous tissue. The cortex was so thin that it was almost indistinguishable or seemed to be lacking altogether. The general effect was to make the corner appear indistinct (Fig. 2, a and k). When the lesion was further developed the defect became definite. It then most commonly took the form of a cleft or crevice just underneath the lattice.\* The cleft included the cortex as well as the shaft. It showed various degrees of development in different cases. In

some the cleft was so slight as to escape observation until especially looked for (Fig. 2, b). In others it extended a short distance into the substance of the bone or even halfway across (Fig. 2, m). In still others, the corner had the appearance of having been torn away from the body of the shaft (Fig. 2, e, f, g, and h). The torn part was the lattice: the tear had occurred through a rarefied zone which could be seen extending beyond the detached fragment. Instead of a cleft, the outer corner was marked in some bones by a triangular area of rarefaction. The cortex adjacent to this appeared extremely thin. The normal contour of the bone was preserved (Fig. 2, i and k). In some cases the outer corner appeared rounded and thrust out beyond the outer end of the lattice and greatly rarefied. The authors have called this phenomenon "*bagging*" (Fig. 2, l).

The inner angle of the radius was affected similarly to the outer angle (Fig. 2 i), but seems much less liable to injury.

The changes in the ulna were more varied than in the radius. Either corner or both were involved (Fig. 2, i, g, and k). The cortex appeared thin or absent and the adjacent cancellous tissue rarefied. The rarefaction was slight and limited to the corner, or assumed a triangular shape and extended some distance into the substance of the shaft (Fig. 2, k). A crack or cleft was often present (Fig. 2, c and j), or the corner appeared torn off (Fig. 2, a and g). The lower end of the ulna was frequently cupped (Fig. 2, d, e, g, i, l, m and n); if the cortex which forms the sides of the cup was thin, the appearance in the x-ray film was that of a halo (Fig. 2, d and h). Halo formation is certainly not characteristic of scurvy, though it was well marked in a number of their cases. In one case the lower end of the ulna showed a spicule shaped like a thorn protruding from the rim of the cup (Fig. 2, o).

When the radius and ulna were viewed together, relationships were noted which seem worth mentioning. In some instances the lattice was torn off at the outer corners of both bones (Fig. 2, f). In others it was torn off at the outer corner of the radius and the inner

\* The lattice is discussed at length in connection with the histology of scurvy. It is sufficient to state here that the lattice is the framework of calcified matrix substance of the cartilage which is responsible for the dense shadow at the end of the shaft. By "underneath the lattice" is meant underneath the dense scorbutic band of shadow which lies across the end of the shaft in the x-ray film.

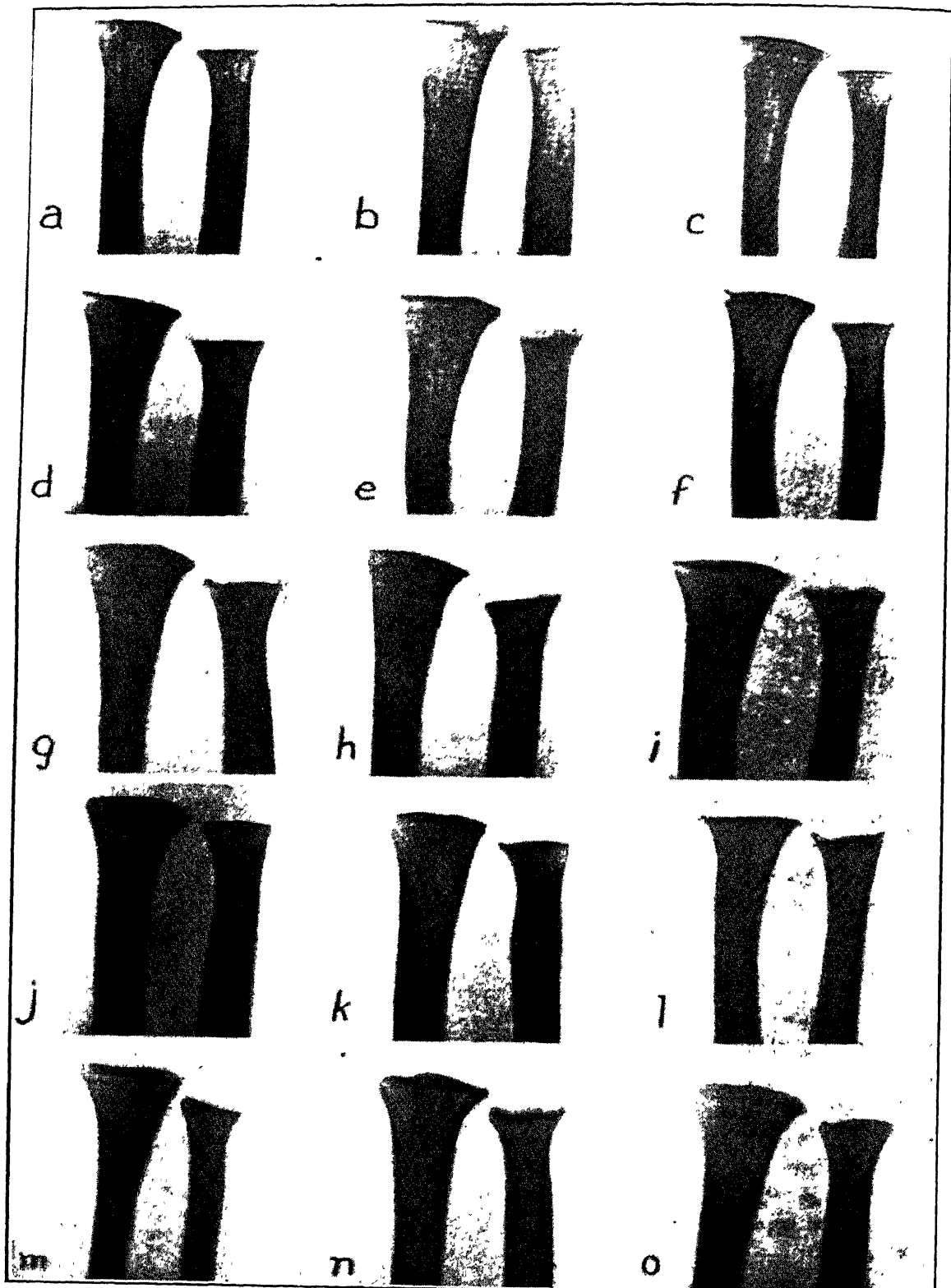


Fig. 2.—For explanation see text. (Park, Guild, Jackson and Bond . Arch. Dis. Childhood )

corner of the ulna. In still others triangular zones of rarefaction were present at the outer corners of both bones (Fig. 2, i), and in yet others, the outer corner of the radius and the inner corner of the ulna were both affected in this way (Fig. 2, k). In a number of cases in which the scorbutic process was probably of longer standing, the end of the ulna and the adjacent part of the end of the radius appeared compressed, whereas the outer part of the radius showed a cleft as if pulled apart (Fig. 2, d, e, m and n). In an extreme case the lower end of the ulna had obviously been crushed to such an extent that the lattice had been absorbed (Fig. 2, e). In another case the lattice had been shifted inwards so that it overlapped the shaft on its inner aspect (Fig. 2, m). The carpal and metacarpal bones showed nothing characteristic.

A method for the *determination of reduced ascorbic (cevitamic) acid content of the blood plasma* has been described by A. F. Abt, C. J. Farmer, and I. M. Epstein (J. Pediat. 8:1 (Jan.) 1936). This method is as follows: Five or more c.c. of blood are withdrawn from a vein and immediately oxalated in a test tube. The blood plasma is deproteinized by the tungstic acid method of Folin, and the filtrate thus obtained titrated against sodium 2:6 dichlorobenzeneindophenol. The authors believe that the values thus obtained for the reduced cevitamic acid content of the blood plasma parallels the intake of vitamin C in the dietary of the patient. Blood plasma values less than 0.75 to 0.80 mg. per cent. of reduced cevitamic acid are considered as evidence of subnormal vitamin C intake. It is believed that this method will prove to be convenient, rapid and accurate for the detection of subclinical scurvy.

**VITAMIN D.**—For those who still question the need for the addition of an antirachitic substance to the *diet of infants*, the experiment of H. M. Barrett (J. Indust. Hyg. 17:199 (Sept.) 1935) is of especial interest. Animals fed a rachitic diet were exposed to ultraviolet irradiation transmitted through varying

degrees of smoke concentration. It was found that irradiation from a quartz mercury arc lamp, after passage through a concentration of smoke, similar to that encountered in the average urban atmosphere, failed to prevent the development of rickets in rats fed on this rachitic diet.

Various methods are being used for adding vitamin D to cow's milk for *infant feeding*. M. G. Peterman and E. Epstein (Am. J. Dis. Child. 50:1152 (Nov.) 1935) suggest that there may be some merit in adding vitamin A as well as D. They have conducted a clinical study to determine the anti-rachitic potency of evaporated milk to which a cod-liver oil concentrate has been added. They also studied the *prevention of scurvy* in this group of infants by the use of **canned ripe pineapple juice** as the sole source of vitamin C. The cod-liver oil concentrate was introduced into the standard evaporated milk during the evaporating process so that each 14½ ounce can of evaporated milk contained 400 units (U. S. P., Revised 1934) of vitamin D and not less than 3200 units (U. S. P., Revised 1934) of vitamin A. Each infant received from 8 to 17 ounces of the evaporated milk per day. No other vitamin D preparation was given. The sole source of vitamin C was from 1 to 2 ounces (30 to 60 c.c.) of pineapple juice per day for each infant. All of the infants made normal gains in weight and length during the period of study. No infant had any clinical, chemical or x-ray sign of rickets or of scurvy during this period, except for 5 infants who had some questionable clinical signs of rickets early in the period; however, there were no positive x-ray findings. The clinical and chemical findings were normal at the end of the period of observation. Peterman and Epstein conclude that by this easy administration of cod-liver oil,

rickets in this group of infants was prevented by 228 units of vitamin D daily in the form of cod-liver oil concentrate in evaporated milk. It is also shown that 1 ounce (30 c.c.) of canned ripe pineapple juice daily provided adequate protection against scurvy until the infants were 6 months of age. Two ounces (60 c.c.) were given after they were 6 months of age.

Further data regarding the antirachitic value of **irradiated evaporated milk** and **irradiated whole milk** in the *prevention of rickets* in infants is available in the reports of M. Rapoport and J. Stokes, Jr. (*J. Pediat.* 8:154 (Feb.) 1936) and T. G. H. Drake, F. F. Tisdall and A. Brown (*Ibid.* 8:161 (Feb.) 1936). Rapoport and Stokes observed no x-ray evidence of rickets over a period of 4½ months during which 2 groups of infants were fed, respectively, **irradiated evaporated milk** containing 125 U. S. P. units of vitamin D per 14.5 ounce can and **irradiated whole fluid milk** containing 140 U. S. P. units per quart. These children received no other antirachitic agents. The authors emphasize that although these milks have adequate protective powers against rickets, they should not be relied upon for the treatment of active rickets. Drake and his associates observed 103 infants whose only antirachitic agent was that contained in irradiated evaporated milk. In contrast to the observations of Rapoport and Stokes, they observed x-ray evidence of mild rickets in 17 per cent. of their infants. This, however, was not of a sufficient degree to cause any great concern from a clinical standpoint. No infant developed moderate or marked rickets.

L. T. Davidson, K. K. Merritt and S. S. Chipman (*Am. J. Dis. Child.* 51:1 (Jan.) 1936) have shown that vitamin D milk from cows fed irradiated yeast, when used in routine feedings as the

sole antirachitic substance, is inadequate for the complete protection of the premature infant against rickets. The authors suggest that the deficiency in vitamin D may be in the first 2 or 3 months of life, when growth is rapid and the intake of milk and consequently of vitamin D is insufficient to prevent the later development of rickets. This later development of rickets, they believe, may be due to the deficiency in the first months of life. It is suggested that the addition of a **supplementary vitamin D feeding** in the early months may be sufficient to protect the infant completely from rickets. In an attempt to answer this question Davidson, Merritt and Chipman (*Ibid.* 51:594 (Mar.) 1936) gave a group of 27 *premature infants* 6 drops of **viosterol** preparation which amounted to 3150 U. S. P. units daily, as the sole *antirachitic* substance. This therapy was started at about the eighth day of life. Ten infants remained free from rickets clinically. The degree of rickets in the other infants was consistently mild and healed satisfactorily by the sixth month. The authors feel that the important question to be answered is whether it is possible to prevent even minor degrees of rickets evidenced in this study by beginning vitamin D therapy earlier than was done in these infants or by increasing the dose in the very early days of life.

Observations on the comparative *antirachitic value* of **crystalline vitamin D** administered in milk, corn oil or in propylene glycol have been made by J. M. Lewis (*J. Pediat.* 8:308 (Mar.) 1936). The experiment was conducted throughout the winter months and 441 young infants were given 145, 290 or 1450 U. S. P. X (revised 1934) units of crystalline vitamin D incorporated in 28 ounces of milk, in 7 drops of corn oil or in 7 drops of propylene glycol. At the end of the winter the incidence of

rickets was determined by x-ray examination of the wrists. It was observed that infants receiving crystalline vitamin D in a daily ration of milk developed rickets less frequently than those receiving a comparable number of units of vitamin D in 7 drops of corn oil or propylene glycol. It was found that 1450 units of crystalline vitamin D in oil was required to prevent rickets, whereas 332 units of crystalline vitamin D per quart of milk had an adequate antirachitic effect.

A clinical investigation to determine the comparative antirachitic potency of irradiated yeast with that of cod-liver oil has been conducted by E. L. Compere, T. E. Porter and L. J. Roberts (Am. J. Dis. Child. 50:55 (July) 1935). The results of their studies indicate that irradiated dry yeast is an effective therapeutic antirachitic agent when given to children in sufficient quantities. The minimum amount of irradiated dry yeast which seemed to effect a cure was 1.25 Gm. (19 grains) per day. This is equivalent to 6755 International or U. S. P. revised units of vitamin D. X-ray observations indicate that it was necessary to give from 1.1 to 3.3 times as many rat units of vitamin D in the form of irradiated yeast as in the form of cod-liver oil to bring about a comparable degree of improvement in *rickets* in children.

In a survey of a large number of institutions dispensing and of many households using **cod-liver oil**, D. V. Whipple (J. Pediat. 8:734 (June) 1936) showed that there is often a failure to observe the precautions necessary to prevent the development of rancidity. While rancidity apparently has little, if any, effect on vitamin D content, it does deplete the quantity of vitamin A. Rancid cod-liver oil may be a factor in the causa-

tion of digestive disturbances. Whipple outlines the following precautions for guarding against rancidity in cod-liver oil: (1) obtain a product in good condition; (2) keep it under refrigeration after the bottle has been opened; (3) keep the mouth of the bottle free from dried residue; (4) obtain a supply sufficiently small to be consumed in a period of 6 weeks or less.

**TETANY.**—An instance of infantile tetany not associated with rickets, and presumably due to a temporary dysfunction of the parathyroid glands, is reported by J. B. Pincus and I. F. Gittleman (Am. J. Dis. Child. 51:816 (Apr.) 1936). The patient, a white infant, 7 weeks of age, was admitted to the hospital because of repeated convulsions during the 24 hours prior to admission. No explanation other than a low blood calcium could be found to account for the convulsions. The calcium concentration in the blood serum was 6.5 mg. per cent. and the concentration in inorganic phosphorus was 8 mg. per cent. When **parathyroid extract** was administered, the serum calcium rose to 11.7 and the phosphorus was reduced to 6 mg. per cent. and the convulsions were controlled. As soon as the administration of parathyroid extract was discontinued, the serum calcium content returned to 5.7 mg. per cent. and the serum phosphorus rose to 6.7 mg. per cent. and there was a return of the convulsions. When parathyroid extract was administered again, similar but less striking results were obtained. Parathyroid extract was discontinued after 120 units had been given and there was no return to the "tetany level." The infant was watched for over a year without return of the convulsions or without a disturbance of the calcium and phosphorus blood levels.

## MEASLES

By ROBERT A. LYON, A.B., A.M., M.D.

A review of the *epidemiology* of measles in London by J. A. H. Brincker (Lancet 1:103 (Jan. 11) 1936) indicated a regularity of incidence of the disease, increasing each year in October and subsiding at the end of spring. The number of measles cases seemed to increase when the percentage of susceptible individuals in a community reached 25, and the epidemic subsided only when the susceptible population decreased to less than 20 per cent. In London, the disease occurred most frequently in children less than 7 years of age; therefore, the methods employed for the prevention of measles must be adapted primarily for the child of preschool age. Quarantine regulations, the closing of schools, and the exclusion from schools of children who had not had the disease had not affected the incidence rate. Hospitalization had seemed to reduce the mortality rates of measles and its complications, but the only method of any apparent value in preventing the epidemics of measles had been the administration of convalescent serum, immune adult serum or placental extracts to susceptible children exposed to the disease.

**Complications.**—An unusual complication of measles, consisting of an increased sensitivity of the skin to cold applications, was described by J. L. Kobacker and H. J. Parkhurst (J. A. M. A. 105:662 (Aug. 31) 1935). Three sisters aged 8, 11 and 13 years, who were recovering from measles, developed an urticaria of any area of the skin which came in contact with cold. This reaction had not occurred before the illness. Cubes of ice placed on the backs of the hands resulted in urticarial wheals within  $2\frac{1}{2}$  to 5 minutes and disappeared within 5 minutes after the cold was withdrawn. Contact with cold water

or glass produced similar results. All 3 children had a slight eosinophilia but no other abnormal finding. This was thought to be the first report of such a complication of measles and was especially interesting because all 3 children of the family were so affected. Within a year after the symptom of urticaria was first noticed, it subsided and gradually disappeared.

**Treatment and Prevention.**—*Placental Extracts.*—Further investigation of the nature of placental extract and its effect in the prevention and modification of measles has been reported by C. F. McKhann, A. A. Green, L. E. Eckles and J. A. V. Davies (Ann. Int. Med. 9:388 (Oct.) 1935). The most reliable test of the amount of the immune bodies present in a solution of placental extract has been the determination of the total nitrogen content. The different globulin fractions of the placental extract contain varying amounts of immune bodies for the different diseases. Diphtheria and scarlet fever antibodies are carried in the more soluble globulin fractions, while measles and poliomyelitis antibodies occur in all fractions, including that obtained from the tissue proteins.

The authors have administered placental extract to 1341 children who were definitely exposed to measles, with the result that 71.5 per cent. of the group were completely protected, 23.9 per cent. developed modified attacks and 4.6 per cent. were apparently not affected by the injections. These figures compare very favorably with the results reported by other investigators with the use of human convalescent serum and are better than those obtained by injection of immune adult serum. The dosage of the placental extract has ranged from 2 to 6 c.c. The reactions caused by the in-



jections have consisted of slight local redness and swelling in 25 per cent. of the group, and severe local reactions in about 4 per cent. of the group. Local inflammation never lasted for more than 3 or 4 days. Systemic reactions included fever in 14.8 per cent. of the group, and urticaria in 3 patients, 2 of whom had had symptoms of allergy previously. There was no serum sickness or local suppuration.

The effect of *oral administration* of the placental extract in preventing or modifying measles was tried in another group of children. The extract was given in doses of 2 to 5 c.c. in ice cold water, about 1 hour before meals, until a total of 9 to 20 c.c. were ingested, the amount varying with the age and size of the child. Of the 18 children who were given the extract in this manner early in the incubation period of measles, 7 were protected, 5 had modified attacks and 6 received no protection. When the extract was given orally to 66 other children late in the incubation period, protection and modification were obtained in two-thirds of the group, but the results as a whole were not as satisfactory as those obtained by subcutaneous or intramuscular injection.

The experience of private physicians with the use of *immune globulin* for the prevention or modification of measles has been reported by E. G. McGavran (J. A. M. A. 106:1781 (May 23) 1936). *Intramuscular injections* of 3 to 5 c.c. of immune globulin were given to 77 patients to prevent measles in some instances and to modify the attack in others, and successful results were obtained in 95 per cent. of the cases. The lack of success in the 5 per cent. of patients was attributed to not giving the globulin early enough in the incubation period or to the insufficient dosage for larger children and adults. To a small group of 16 patients, 12 c.c. of the

immune globulin was administered *by mouth* in doses of 3 to 4 c.c. in ice water before breakfast. Failure to obtain the desired results was recorded in only 2 instances, but the success of this method of treatment was difficult to determine; it seemed to the author that it was not as effective as the intramuscular injections. Mild local reactions occurred in about one-third of the patients who received the immune globulin intramuscularly and slight febrile reactions were noted in one-sixth of the group.

The availability of immune globulin makes it a much more practical material for general use in rural practice than convalescent serum or immune adult serum, but it is necessary to administer it early in the incubation period if complete protection from disease is desired, and the dosage must be adjusted to the size of the patient, larger amounts being required for adults than for children.

The death rate of measles decreased in the community during the time immune globulin was used, and although the mortality rates of measles in the whole state had decreased during the past 3 or 4 years, it was believed that the immune globulin was an important factor in modifying the local epidemic of that disease.

*Placental extracts* have been used with success by I. M. Levitas (*Ibid.* 105:493 (Aug. 17) 1935). Seventeen patients who were exposed to measles were immediately given 2 c.c. and 1 infant less than a year of age received 1 c.c., with the result that 13 children who had had intimate exposures developed modified attacks of the disease, and 2 other patients with only a moderate degree of contact were completely protected. In 3 other instances the inoculations were given on the fifth day after exposure, and in these patients the disease ran its usual course. In 12 children exposed to

measles in the hospital wards 3 c.c. of the immune globulin were injected within 2 days after contact, and all of these children were completely protected against the disease. Local reactions were mild and none of the patients had systemic reactions or any allergic manifestations.

Among other reports of the successful use of *immune globulin* for the prevention or modification of measles was that of G. M. Laning and T. N. Horan (J. Michigan M. Soc. 34:772 (Dec.) 1935). They administered 2 to 10 c.c. of the material to 19 children during the first 4 days after exposure to measles; 12 of this group were protected against the disease, while the remainder had mild attacks. The immune globulin was given in doses of 2 c.c. to 74 exposed patients in order to modify the attacks and 68 of the group developed mild measles and 6 had moderately severe forms of the disease. As a comparison, the authors cited a series of 46 patients who had received no treatment and had contracted measles in its usual forms. Eleven of these had moderately severe symptoms, 26 had severe attacks, and 2 died.

Better methods of *standardization and purification* of the *placental extracts* were thought to be necessary by S. Karelitz (New York State J. Med. 35:876 (Sept. 1) 1935) to make the material satisfactory for general use. Numerous reactions occurred in the group of 64 children

treated with *immune globulin*. A total number of 34 patients had reactions, including .5 instances of severe local tenderness; 8 had general reactions with fever; and in 3 cases allergic manifestations consisting of urticaria or asthma were observed. Because of these reactions, convalescent serum or adult immune serum seemed preferable to placental extracts. However, it was thought that further refinement of the placental extracts might eliminate proteins causing these reactions.

**Immunity.**—Some question has been raised from time to time regarding the effectiveness of modified measles in conferring permanent immunity on the patient. This subject has recently been investigated by J. H. Townsend (New England J. Med. 214:732 (Apr. 9) 1936). About 10 years ago, 32 students who were exposed to measles received 9 c.c. of convalescent whole blood approximately 8 days before the development of the measles rash. Up to the present time none have suffered a subsequent attack of the disease, although a few of them had been in close contact with it on several occasions and others have been in schools or colleges where there was ample opportunity for exposure. It was felt certain, therefore, that an attack of measles which had been modified by the injection of **convalescent serum** during the incubation period conferred a permanent immunity upon the patient.

## DISEASES OF THE NEWBORN

By ROBERT A. LYON, A.B., A.M., M.D.

**CONGENITAL DEFECTS.**—The incidence of congenital defects of newborn infants in families in which there was already one such infant was the subject of an investigation by D. P. Murphy (J. A. M. A. 106:457 (Feb. 8) 1936).

Statistics were gathered from the death certificates of a 5-year period and in every instance in which a congenital defect was the chief or a contributing cause of death, the history of that patient was obtained by home visitation

and the inspection of hospital records. There were 275 families found to possess more than one congenitally malformed child. In families with one congenitally deformed child, deformities occurred in 1 of 8.9 of the subsequent live births. In the population at large, congenital abnormalities were noted in only one in every 213 live births. Parents of a child with a congenital malformation often ask whether the next children will be normal. The author stated that statistics indicated that there would be 24 times more possibility of a second congenitally malformed child than under normal circumstances.

In a subsequent investigation D. P. Murphy (Am. J. Dis. Child. 51:1007 (May) 1936) studied the relationship between the *maternal age* at the time of conception and the incidence of congenitally malformed infants. Material was obtained from the records of 607 congenitally malformed children and 1583 normally developed siblings. From the analysis of these statistics it was concluded that the proportion of defectives to normal offspring was lowest when the mothers were between 20 and 25 years of age, and the proportion tended to increase when the mother passed the age of 30 years and was greatest in mothers more than 40 years of age. Congenital malformations were found most frequently in infants who were fifth or more in order of birth.

**NORMAL CONSTITUENTS OF BLOOD.**—Several investigations of the average values of some of the blood elements of normal newborn infants have been made during the past year.

The number of *platelets* in the venous plasma of newborn infants varies between 500,000 and 600,000 per c.mm. during the first 10 days of life, according to E. I. Leslie and H. N. Sanford (*Ibid.* 51:590 (Mar.) 1936). The quantity does not change from day to day, but

qualitative differences are apparent because the platelets resist disintegration until about the fourth day of life. After that, the disintegration is greater than at time of birth and it was thought probable that prothrombin was produced by disintegration and this influenced the coagulation time of the blood. The resistance of platelets to the disintegration occurred at the same time that an increase in coagulation time of the blood was noted during the first few days of life.

The average amounts of *fibrin* in the 100 c.c. of plasma varied from 0.22 to 0.67 grams, with an average value of 0.38 grams, according to M. M. Crane and H. N. Sanford (*Ibid.* 51:99 (Jan.) 1936). A slight rise in the quantity of fibrin took place during the first 3 to 5 days of life, but remained stationary during the next 5 days. The fibrin values probably give a fairly accurate indication of the amounts of fibrinogen present. In the study of the fibrinogen content of the blood of newborn infants, Crane and Sanford (*Ibid.* 51:311 (Feb.) 1936) noted that the intramuscular administration of uncitrated whole blood did not affect the fibrinogen values, and, therefore, the injected blood apparently influenced some other constituent than fibrinogen in its anticoagulant effect.

Determinations of the *cholesterol content* of normal newborn infants have been made by W. M. Sperry (*Ibid.* 51:84 (Jan.) 1936). In a group of 63 normal infants 4 to 25 days of age, the total cholesterol values varied from 71 to 190 mg. per 100 c.c. The range for adults was 130 to 350 mg. per 100 c.c. It was found that the total cholesterol content of the plasma increased considerably in the first 3 or 4 days of the infants' lives, an increase which was greater than could be explained by dehydration and concentration of the blood

plasma alone. There seemed to be no relationship between the jaundice of the newborn and the cholesterol level. The percentage of combined cholesterol to the total cholesterol was 41 to 72 in infants and 70 to 75 in adults, but there was a tendency for the ratios in infancy to increase with advancing age. It was concluded that the regulatory mechanism which maintains cholesterol at a fairly uniform level in adults is not well established in the first few weeks of an infant's life.

#### ICTERUS NEONATORUM.—

The variations of the *icteric index* in the newborn in relation to the clinical manifestations of jaundice have been investigated by B. E. Bonar (Am. J. Dis. Child. 50:1143 (Nov.) 1935). The capillary method of Davis was employed to make the determinations of the icteric index of the cord blood and subsequently of venous blood of 104 infants on each of the first 12 days of life. The icteric index at birth was about twice that of a normal adult and rose for the first 5 days to levels of about 53 and then declined until at the age of 12 days, when the infant had an index about twice that noted at birth. Clinical jaundice did not usually appear until the icteric index reached about 30 per cent., but occasionally there was no clinical icterus when the levels were as high as 60. About 70 per cent. of the group had clinical jaundice and the icteric index in these infants was generally higher than the average figures and, like the group as a whole, the peak was reached on the fifth day and gradually declined to levels of about twice that at birth by the twelfth day. The 30 per cent. of infants who were not jaundiced throughout their first 12 days of life had lower icteric index levels and tended to return to birth levels by the end of the twelfth day. There was no relationship discovered between the icteric index and

the sex of the patient, the coagulation or bleeding time, or the duration or type of delivery. However, the overweight infants had lower icteric indices than the general average.

Determinations of the *hemoglobin* and *erythrocyte* levels were made on the third, sixth and ninth days of the infant's life. During this period there was a rapid rise and fall of the icteric index with but little change in the levels of hemoglobin or red cells, which led the author to conclude that icterus neonatorum was not due entirely to the destruction of erythrocytes in the early days of life. *Hemolysis* of the blood occurred in 44 per cent. of the samples taken, was least noticeable in the cord blood, and was greatest at the end of the first day. Hemolysis was uncommon in infants with a high bile index and did not seem to be related to the erythrocyte counts, the coagulation or bleeding time or the hemoglobin content of the blood, or to the type of delivery, although it occurred with slightly greater frequency in infants born spontaneously and of labors of normal duration. Three infants not included in the above group were jaundiced at birth. Two of these died within a short time with low hemoglobin and erythrocyte determinations. The disease was apparently not the result of an obstructed bile tract or hepatitis but, it seemed to be due to a hemolytic anemia.

In a study of the number of *erythrocytes* of the newborn in relation to icterus neonatorum, L. C. Martin and S. M. Evans (Arch. Dis. Childhood 10: 355 (Oct.) 1935) found no significant differences in the average number of red cells per cubic millimeter in children who became icteric within the first 2 or 3 days of life and in those who did not. Hemoglobin values were about the same in the 2 groups of infants. When subsequent daily erythrocyte counts were

made for 5 days after birth, it was found that the infants who developed icterus neonatorum had higher counts than the average of the total group or the average of those who did not develop icterus, but it was impossible to predict from the blood count in an individual case, which child would develop icterus and which would not. The authors believed that the presence of icterus was a result of a disturbed balance between the production and the destruction of the red blood cells.

The *prevention of jaundice* of the newborn by **immediate tying of the umbilical cord** at birth was attempted by N. Book (Canad. M. A. J. 33:269 (Sept.) 1935). In a group of 200 infants, the cord was tied immediately at birth and in 200 other infants the cord was not tied until pulsation had ceased for 3 to 4 minutes. In the first group only 32 per cent. of the infants developed jaundice and none was jaundiced at time of discharge from hospital. In the group in which the cord was not tied for several minutes, 73 per cent. developed jaundice and 29 per cent. were jaundiced at the time of discharge from the hospital. Clotting and bleeding times were approximately the same with both types of treatment of the cord and there was no apparent difference in the gain in weight and general health of the infants of the two groups. The order of birth of the infants and the sex did not seem to have any influence on the occurrence of jaundice in either group. The administration of such drugs as quinine and nembutal to the mothers had no influence on the incidence of jaundice in their infants. All of the prematures in the two groups were jaundiced. It was the opinion of the author that the immediate tying of the cord prevented a large amount of blood from entering the infant's body, thus preventing the occurrence of a polycythemia or in-

creased fragility of these cells, which seemed to be factors in the development of jaundice.

A review of the subject of *icterus gravis neonatorum* and a typical case-history was reported by I. P. Sobel (Am. J. Dis. Child. 51:104 (Jan.) 1936). The infant which he observed was normal at birth, except for the jaundice which increased in intensity during the next few days as the patient became somnolent and very ill. The liver was enlarged and there was a marked anemia with large numbers of normoblasts present. With several **blood transfusions** the child's condition improved and the number of red cells returned to normal figures, the normoblasts disappeared from the blood, and the child became entirely well, except for a marked opisthotonos. From a review of the medical literature of the last few years, the author noted that the characteristic pathologic changes reported in icterus gravis neonatorum have consisted of the persistence of *hemopoietic centers in the liver and spleen, kidneys*, and occasionally in other organs. The retention of bile in the liver was thought to be due to (1) damage of liver cells, so that the large amounts of bilirubin could not be excreted; (2) a bile which has become too viscous to pass through the small bile ducts; or (3) the accumulation of bile, leading to its coagulation within the bile passages.

Clay-colored stools, especially at the beginning of the disease, was one of the common *symptoms*. Icterus gravis has been found to be familial in many instances but sporadic cases have been reported. The anemia is characteristically the hyperchromic type and the number of nucleated red cells are often greater than usual in infancy, the normal figures at this age being 5000 per c.c. or less. There is a tendency for the nucleated red cells to decrease in number

as the child grows older and the absence of such a cellular reaction does not exclude the diagnosis of icterus gravis. The number of white cells is usually increased and occasionally there is an eosinophilia. Somnolence is a frequent symptom and sometime severe convulsions and intracranial hemorrhage have been encountered in this disease.

The *cause* of icterus gravis is generally thought to be the persistence of extra-medullary hematopoietic centers in the liver, spleen and other tissues, which leads to an increased production of red cells. The other theory is that some factor causes an unusually rapid destruction of red cells, which results in the persistence of these hematopoietic centers to aid in maintaining an adequate number of red blood cells.

The most satisfactory *therapy* consists of **blood transfusions** and injections of **dextrose solutions** to sustain the infant until the process of blood destruction subsides. Early treatment of this type offers a much better *prognosis* of this disease than was formerly thought.

The relationship of *obstruction of the passage of bile* to icterus gravis has been discussed by S. G. Ross and T. R. Waugh (*Ibid.* 51:1059 (May) 1936). They reported the histories of 6 infants with icterus, usually of the hemolytic type, accompanied by symptoms of obstruction of bile flow. Both of these factors seemed to influence the severity of the icterus gravis. The hemolytic features and severe anemia were usually noted before the child was more than 2 days old, indicating that the pathologic process had started *in utero*. The excessive hemolysis in these infants was accompanied by an increase in the blood of the numbers of reticulocytes, polychromatophilic cells and erythroblasts of various types. The occurrence of these cells seemed to be dependent upon

the severity of anemia and the time of its development, and seemed to be a response to a call for blood rather than forms of a specific erythroblastic anemia. The cause of the hemolysis is not known, but the authors were inclined to agree with Parsons that there was some factor in the blood of the mother or infant which induced hemolysis and that the embryonic cells appearing in the peripheral blood were the results and not the cause of the anemia. The occurrence of obstruction in the bile ducts tended to increase the intensity of the icterus and when this condition was marked, it sometimes led to hemorrhagic disease and to a cerebral accident. Jaundice due entirely to obstruction seemed to be less common than jaundice due to hemolysis and although the course of these two conditions was by no means parallel, they were frequently associated in the same patient, and as one improved, the other often remained stationary. The recognition of these two factors in an infant with jaundice was thought to be especially important when the type of therapy was considered. **Blood transfusions** are indicated in *hemolytic types* of jaundice, while in *obstructive types* of jaundice, without any accompanying anemia, **dietary treatment** was preferable.

**BLOOD DYSCRASIAS.**—Four instances of *erythroblastosis* in newborn infants were described by H. S. Andrews and A. J. Miller (*Am. J. Dis. Child.* 50:673 (Sept.) 1935). These infants were noted in a group of less than 2000 births with an incidence rate of 1 in 490. Two of the patients were negroes and were the first cases of erythroblastosis in that race to be reported. Characteristic features of the disease were enlargement of the liver and spleen, a moderately severe anemia, and an increased number of nucleated red cells and leukocytes. Early forms of the

myeloid series occurred in 1 to 8 per cent. of the patients; jaundice was present in every instance; and hemorrhages occurred in 2 infants. Two of the patients died and the findings at autopsy included the presence of hematopoietic centers in the liver, kidneys, spleen and pancreas; hyperactive bone-marrow; hemorrhages through the body; and in the kidneys, lungs, and skin there were large atypical epithelial cells, the origin of which was not known.

An unusual case of *congenital thrombocytopenia* was reported by H. N. Sanford, E. I. Leslie and M. M. Crane (*Ibid.* 51:1114 (May) 1936). The mother of the patient had had purpuric rashes frequently during her lifetime and several other members of her family had had similar lesions without impairment of their health, so that the appearance of this symptom in her newborn infant caused her no alarm. Both the mother and child has a considerable reduction in the number of platelets, but the platelets of the child returned to normal figures by the end of 10 days. The absence of severe hemorrhage was thought to be due to the fact that the platelets disintegrated rapidly and provided material for the clotting process.

**TETANY.**—Tetany in the newborn has been observed with increasing frequency during the past few years. *Hyperventilation* has been suggested as one of the contributory causes of the tetany syndrome by W. R. Shannon (*Arch. Pediat.* 52:501 (Aug.) 1935). The tendency of newborn to breathe deeply, with each successive respiratory movement deeper than the one preceding it, is a mechanism for the expansion of the lungs leading to hyperventilation. *Anoxemia* is another condition thought to be related to tetany. Hyperventilation and anoxemia seem to cause a disturbance of the ionization of calcium. Many instances of tetany in the newborn have

been confused with atelectasis, brain injury, and asphyxia, and in such cases tetany was possibly caused by an increased sensitivity of the respiratory center so that small amounts of carbon dioxide stimulate frequent respiratory movements.

The treatment of patients with cyanosis and symptoms of tetany has consisted of the administration of **carbon dioxide** and **oxygen**, and this treatment was thought to be effective if it is given continuously. Several infants observed by the author had the symptoms of hyperventilation associated with an output of urine which was more alkaline than normal for this age period. Cyanosis was observed in 5 of the 8 cases which were reported and the administration of **carbon dioxide** and **calcium** to these patients brought about rapid recovery. Premature infants in their baskets or incubators often rebreathe an air which has a high carbon dioxide content and this may be one reason for the success of that type of care for such infants.

A typical example of tetany in an infant 8 days old was reported by I. Starin (*Ibid.* 52:489 (July) 1935). Symptoms consisted of frequent convulsions, hyperirritability and attacks of cyanosis. The blood calcium was 6.8 mg. per cent. Following the administration of **calcium gluconate**, **viosterol** and **ultraviolet light**, the infant made a complete recovery and the blood calcium rose to 10.3 mg. per cent. within the following 6 weeks. No cause for this condition could be determined.

A case of tetany in a newborn infant which was observed by J. L. Rothstein (*J. A. M. A.* 105:1189 (Oct. 12) 1935) had very few of the classic symptoms of that disease. Symptoms of a projectile vomiting and a painful cry of colic and an unusual type of subcutaneous edema led to the determination of the blood

calcium which was found to be 7 mg. per cent. A positive Chvostek's sign was present, but there were none of the twitchings or convulsions usually characteristic of the disease. It was suggested that many of the customary signs indicative of tetany in older children may not be present in newborn infants.

**HYPOGLYCEMIA.**—Symptoms resembling tetany may be produced by hypoglycemia. Two instances of hypoglycemia in newborn infants were reported by R. A. Higgons (*Am. J. Dis. Child.* 50:162 (July) 1935). In one instance the patient developed convulsions on the second day of life and in the other within the first 24 hours. Sugar in the blood measured 47 and 50 mg. per cent., respectively, and treatment with a glucose solution caused rapid improvement. The mother of one child was a known diabetic and had taken insulin at irregular intervals during the prenatal period. On the day of the delivery she had taken 25 units, but it was questionable whether this had any effect on her newborn infant. It was the opinion of the author that conditions of hypoglycemia may be relatively common in the newborn. Considering the fact that children take food poorly, especially when severe hypoglycemia develops, it was considered important to administer sugar by gavage or by parenteral methods in order to correct the condition.

**DISEASES OF CENTRAL NERVOUS SYSTEM.**—The *Moro reflex* in an infant consists of a movement of the arms to a position of embrace, as if it were grasping for support, following certain stimuli such as falling a short distance of 2 feet or less, sudden motion of the blanket or sheet under them, or sometimes loud noises. The interpretation of this reflex has been discussed by W. Dennis (*Am. J. Dis. Child.* 50:888 (Oct.) 1935). The posi-

tive test was originally described as a normal reaction of an infant of 3 months of age or less, and the absence of the reflex at this age has been considered as an indication of an intracranial lesion. When older infants had a positive Moro reflex, they were usually thought to be retarded mentally or to have some injury within the brain. According to the author, this test has many variations and many types of stimulus will produce the reaction in newborn infants. It was his opinion that under certain conditions a positive reflex may be obtained for many months after the child is born. The elicitation of response seemed to depend considerably upon the amount of relaxation of the child, and older children in this state often gave positive responses which became negative as soon as the patients became tense and were expecting the stimulus. In retarded children, the adaptation of expectation is usually decreased and hence the Moro test may be an indication of delayed mental development; the author believed, however, that groups of other types of intelligence tests were much better indications of mental development.

The *appearance of the fundi* and the *optic discs* of 150 newborn infants have been described by S. Karelitz and P. Vogel (*Ibid.* 50:872 (Oct.) 1935). These infants were observed during the first 10 days of life and a large number of them were observed for a period of several months thereafter. The fundi were paler than those of adults and the vessels of the choroid could be seen very distinctly, possibly because of the lack of pigmentation of the retina. The central vessels were narrow and it was often difficult to distinguish between the arteries and veins in the very young infants. The optic nerve head was less pigmented and had a definite gray tint. In 87 per cent. of the infants it was considerably different from that of the



adult. Both the fundus and the optic nerve head were paler in the blonde infants than in the brunettes or in infants of the negro race. In premature infants the color was paler than in the full term babies. Changes in the appearance of the optic disc and fundus took place within 2 weeks to 6 months. After 2 months 50 per cent. of the infants had developed the color and other characteristics of the adult fundus and optic disc, and at the age of 3 months 60 per cent. resembled the adult type. The pallor of the fundus persisted for a longer time than the gray color of the optic disc. The authors emphasized the fact that the characteristics of the normal infant's eyes should be borne in mind before a diagnosis of optic atrophy is made in the newborn infant. In 4 instances hemorrhagic areas were noted in the fundi and in 2 of these infants there was complete absorption within a period of 1 week. There seemed to be no relationship between the appearance of the optic nerve and the sex of the infant, the order of birth, or the severity of labor. The natural change of the color of the fundus and disc as the infant grew older was thought to be due to an increase of vascular supply and to a natural process of pigmentation of the retina.

An unusual type of *meningitis* was reported in a newborn infant by J. D. Craig and L. L. Mackenzie (J. Pediat. 8:434 (Apr.) 1936). In the cerebrospinal fluid was found a *bacillus acidilactici*. The child had a purulent discharge from the ear from which a streptococcus was recovered and a terminal pneumonia, probably due also to a streptococcus infection. Only 4 instances of meningitis caused by this organism have been reported previously, 3 of these in newborn infants and 1 in an adult. All of the patients died.

#### GASTROENTERIC DISEASES.

—The incidence of *gross or occult blood*

*in the stools* of 107 newborn infants was determined by B. E. Bonar (Am. J. Dis. Child. 51:255 (Feb.) 1936). The data were gathered from the examination of 3539 stools of these patients during the first 10 days of life. A positive benzidine reaction was obtained in 55 per cent. of the specimens and no infant had less than 7 stools which contained occult blood. Blood was most frequently found on the third, fourth, and fifth day of the infants' lives. A search was made for sources of this blood and conditions associated with its occurrence. Occult blood was found in only 3 per cent. of the 989 samples of breast milk tested. It occurred most frequently on the second to fifth day, but never was found in more than 6 per cent. of the samples of milk at any one time, so that bleeding of the nipples could not be considered as an important source of blood in the stools. No relationship could be established between the occurrence of occult blood in the stools and the sex of the infant, its initial loss of weight, the type of labor, the erythrocyte and hemoglobin levels, or the occurrence of jaundice. Blood was more common in the stools of infants taking larger amounts of food, either because this led to mechanical irritation of the intestinal tract or introduced large numbers of bacteria. The heavier babies and those with prolonged bleeding and coagulation times had blood more frequently in the stools than did the other infants. The author concluded that bleeding during the first few days of life was probably caused by rupture of blood vessels of the intestinal mucosa which had become engorged by pressure and asphyxia during the birth process. Later, a mild inflammation of the intestinal tract when bacteria and food first entered, seemed to cause bleeding, especially at a time when the bleeding and coagulation times were prolonged.

Two instances of *gastric ulcer with fatal hemorrhage* in newborn infants were reported by R. H. Kunstadter and E. Gettelman (J. A. M. A. 106:207 (Jan. 18) 1936). Hematemesis of bright blood in the first 36 hours after birth occurred in both patients, melena in only 1 case. One of the infants had a duodenal atresia and the persistent vomiting was thought to have had some bearing on the etiology. In neither instance were microorganisms found in the study of the pathologic sections. Transfusion of whole blood did not aid the condition and it was concluded that hemorrhagic disease was not the cause of the bleeding in these patients.

A *duodenal ulcer* in a newborn infant followed by *perforation* on the fourth day of life was reported by F. Seinsheimer (*Ibid.* 105:875 (Sept. 14) 1935). An infant delivered by Cesarean section suddenly developed symptoms of shock when it was 4 days old, the abdomen became distended, and death occurred within a few hours. At necropsy the peritoneal cavity was found to be filled with a yellow fluid which had apparently resulted from the exudation of material through the perforated ulcer and from an acute inflammation of the peritoneum. Only 12 instances of rupture of duodenal ulcer in infants less than one year of age could be found in the medical literature.

**HEART DISEASE.**—*Tachycardia* noted before the birth of an infant was reported by L. E. Farr and M. E. Wegman (Am. J. M. Sc. 190:22 (July) 1935). A heart rate of 140 to 160 was noticed shortly before the birth of the child, but tachycardia did not occur again until the child was a little more than 3 weeks of age. Several other attacks occurred during the next 5 months of the child's life, but each one was of less severity than the preceding one, and after that time the child seemed

to be entirely normal. X-rays showed an increased width of the hilar shadows and some increase in the peripheral markings which were present for about 10 days after the child first developed the paroxysmal tachycardia. The electrocardiogram taken during an attack indicated a cardiac rate of 300, a normal rhythm, left axis deviation according to new terminology, and some variations in the size of the T-waves in lead one. No definite cause of the lesion could be found and no treatment seemed to be effective in slowing the rate, although digitalis was used on each occasion.

The significance of *cardiac enlargement* is difficult to estimate in the newborn. X-ray examinations were made of 3 newborn infants with symptoms of cyanosis and dyspnea by S. Liebe (Monatschr. f. Kinderh. 64:48 (Nov.) 1935). Enlargement of the heart was noted at first, but within a few days the heart became smaller and the symptoms disappeared. One of the patients had a congenital heart lesion, but the cardiac shadow in this case, likewise, became smaller after a short period of time. It was the opinion of the author that the extra load on the circulatory system, which occurred at the time of birth of the child, frequently produced cardiac enlargement, together with the symptoms of cyanosis and dyspnea, but this syndrome need not always be considered serious, because improvement could be expected in most instances without any specific treatment. (For further discussion of congenital cardiac disease, see Heart Disease in Children.)

#### **GENITOURINARY DISEASE.**

—A series of 61 newborn infants with urinary symptoms were reported by W. S. Craig (Arch. Dis. Childhood 10:337 (Oct.) 1935). In the urine of 48 of this group pus cells were present in large numbers and in 13 hyaline or granular casts were observed. Cultures

of *B. coli* were obtained in 7 patients and in 4 of these, various types of streptococci were also found. In 3 instances positive cultures were obtained from urines which did not have an increased number of pus cells. The urines of the healthy newborn were found to contain a few casts or cells and occasionally some red blood corpuscles, and in 10 of a group of 43 specimens which were examined bacteriologically, *B. coli* or some type of staphylococcus or streptococcus was found. *Symptoms* which suggested some urinary disturbance were, in order of frequency: fever, anuria or marked diminution in urinary output, thirst, restlessness or irritability, a dusky, gray appearance of the face, sweating, vomiting, sudden collapse, edema and convulsions. The usual symptoms were a slight fever beginning on the second or third day of life, with occasional vomiting or anuria. The amount of urine excreted was frequently diminished so that only 2 or 3 diapers would be moistened within the first 36 hours and urine could not be obtained from the bladder by catheterization of these patients. At necropsies of 6 of these infants, a suppurative pyelonephritis was found in one instance, the presence of pus cells in the kidney tubules with congestion of the pyramids in 5, a leukocytic infiltration in 1, and a hemorrhage into the interstitial tissue in 1, uric acid infarcts in 2 instances, and a congenital abnormality of the kidney was found in 1 patient. In many instances it was felt that severe infections of the intestinal tract or intracranial hemorrhage might be etiologic factors leading to the occurrence of urinary disturbances.

In regard to *treatment*, the authors found that the administration of **fluids**, especially of **weak tea** and **alkaline solutions**, was beneficial in promoting the flow of urine. A follow-up of a

number of children who had urinary disturbances at birth indicated that recovery was usually complete and remissions were rare.

**RESPIRATORY DISEASES AND RESUSCITATION METHODS.**—The subject of *pneumothorax* in the newborn has been reviewed by J. Glaser and D. B. Landau (Am. J. Dis. Child. 50:986 (Oct.) 1935). They were able to collect 16 reports of this condition in the newborn and added a case which they had personally observed. Previous writers have found 300 such cases occurring in children under 12 years of age. In the group of 17 infants in which the condition occurred within the first few weeks of life, the mortality was 47 per cent., and more than twice as frequent in male as in female infants. The *mortality* in children of older ages was reported to be about 60 per cent. so that the newborn infant apparently withstood this condition better than the older child. The common *symptoms* of this lesion were dyspnea and cyanosis, which were accompanied by physical signs of hyperresonance of a portion of the thorax and the diminution of breath sounds in that area.

By means of the x-rays and fluoroscope, the *diagnosis* may be made more accurately by noting the differences in the height of the diaphragm on the two sides, the absence of the pulmonary markings, and the shifting of the mediastinum and its contents. Intrapulmonary injection of an opaque oil was helpful in making the diagnosis in about 40 per cent. of the patients reported. Other conditions which frequently resemble pneumothorax in the newborn were pneumonia, atelectasis, massive collapse of the lung, congenital cyst of the lung and congenital hypoplasia of the lungs.

The chief *causes* of pneumothorax in the newborn were thought to be infec-

tions, congenital defects and trauma. Some of the rougher methods commonly employed in establishing respiration of the newborn were thought to be capable of producing pneumothorax.

*Treatment* of pneumothorax in this age group consisted in **eliminating the cause**, if possible, and in **removing the air from the pleural cavity**.

The aspiration of mucus is the most common *cause* of *cyanosis* in the newborn, according to E. A. Morgan and A. Brown (J. A. M. A. 105:1085 (Oct. 5) 1935). Other lesions responsible for cyanosis are atelectasis, cerebral edema, intracranial hemorrhage, persistent enlargement of the thymus and tetany. In preventing the aspiration of mucus or in treating the condition, mistakes have been made such as (1) a delay in removing the mucus until after the first inspiration of the infant; (2) the use of a coarse gauze to wipe out the mucus from the mouth, which is ineffective and apt to cause trauma of the mucous membrane; (3) the vigorous use of a hard catheter for the aspiration of mucus, which tends to traumatize the pharynx and often helps to introduce organisms into the air passages.

The most satisfactory method of removing the mucus was thought to be a **suction apparatus** of moderate force and equipped with a metal suction tip with smooth surfaces and bent to conform with the natural curvature of the infant's mouth and pharynx.

The diagnosis of atelectasis, prohibiting the proper aeration of blood in the lungs, another cause of asphyxia, depended upon x-ray examination in most instances. Cerebral edema was thought to be the cause of cyanosis in some instances and was usually due to birth trauma. The diagnosis of intracranial hemorrhage has been made often on unreliable signs such as abnormal reflexes, disturbances of muscle tone, and xantho-

chromic or bloody cerebrospinal fluids, but of more significance are asphyxia pallida, difficulty of deglutition, stertorous breathing, a full and boggy fontanel, convulsions, the presence of gross blood in the cisternal fluid and lesser amounts in the spinal fluid, prematurity and the history of a difficult or instrumental delivery.

The method of *resuscitation* of the newborn selected by J. F. McGrath and K. Kuder (*Ibid.* 106:885 (Mar. 14) 1936) was the introduction of a tube into the larynx of the infant by direct laryngoscopy, removal of mucus and other fluids by suction and insufflation of a mixture containing 90 to 95 per cent. of **oxygen** and 5 to 10 per cent. of **carbon dioxide**. The failure of a newborn infant to breathe properly was considered to be due to (1) immaturity of the patient, (2) intracranial injury or pressure, (3) depression of the respiratory center by narcotics, a lack of oxygen or excess of carbon dioxide, and (4) to some peripheral lesion, such as obstruction of the larynx, unexpanded alveoli, circulatory failure and the like. Among 4865 consecutive deliveries, 226 or 4.4 per cent. were found to require resuscitation.

The *treatment* consisted in (1) the **removal of obstruction of the air passages**, (2) **insufflation or distention of the alveoli**, and (3) **stimulation of the respiratory center**. Drugs as stimulants of the respiratory center were found to be of very little value. **Handling the baby gently** and without haste was thought to be the first principle of treatment. Stimulation of peripheral nerves by some method, such as **slapping the soles of the feet** and the **removal of fluid from the mouth with sterile gauze** will often suffice in stimulating respiratory movements. Mouth-to-mouth breathing or pressure insufflation with a pump were thought

to be dangerous in some instances. **Respirator machines** occasionally were helpful, but had definite limitations of usefulness. The introduction of the **laryngoscope** followed by the **removal of fluid from the trachea and bronchi**, and **insufflation of oxygen and carbon dioxide**, with little or no pressure, seemed to be the most effective method of treatment. When this method was unsuccessful in stimulating breathing, none of the others were found to be effective. In a few instances, trauma of the pharynx and larynx, with excoriation and edema, were noted but never were these lesions serious enough to cause the death of the infant.

**PREMATURITY.**—It has been noted that most newborn infants secrete large amounts of estrin in their urine during the first few days of life, and premature infants have, therefore, been deprived of this intrauterine stimulation for a month or more, which may account in part for their unstable metabolic mechanism. **Estrin** was administered to a group of premature infants and the results of growth and weight gain were compared with those of a control series by A. Moncrieff (Arch. Dis. Childhood 11:9 (Feb.) 1936). Estrin prepared in the form of trihydroxyoestrin in olive oil and ketohydroxyoestrin in aqueous solution was administered subcutaneously in doses of 100 units per pound of body weight for 7 days. The control group received injections of olive oil or water only. The feeding and care of the 2 groups was otherwise the same. The weight gains of 80 treated infants at the end of 7 to 14 days were slightly greater than the control infants, but the differences were small and inconclusive. Girl babies gained more rapidly than boy babies with this treatment. The authors could not recommend the estrin injections as a routine measure for the treatment of premature infants.

By the injection of benzidine into the *capillaries of the brain and liver* A. M. Mali and C. E. Ráihá (Acta Paediat. 18:118, 1935) observed that the small vessels of premature infants were more fragile, were smaller in size, less numerous, and spaced wider apart than in full term infants. Such conditions were thought to lead to disturbances of oxidation in the tissues, resulting in the lowered metabolism, a tendency to acidosis, an unstable heat mechanism, and the attacks of asphyxia in the first few days. The wide separation of capillaries in the medulla might account for the irregularity of respiration of premature infants and might even lead to impairment of mental development and function. Similar arrangement of the liver capillaries might cause disturbances of function of that organ and influence the occurrence of icterus neonatorum. The capillary network was thought to have its greatest development in the last 3 months of fetal life.

**MISCELLANEOUS.**—Among numerous reports of abnormalities of the newborn, the following were of interest.

A *congenital bony temperomandibular ankylosis* was reported in a newborn infant by L. W. Burket (J. A. M. A. 106:1719 (May 16) 1936). The left side of the face was malformed, with a depression below the zygomatic arch and the rudimentary mandible. The joint was freed by surgical procedures 24 hours after birth, but bony ankylosis occurred at the age of 2 months and only a small aperture between the jaws remained which allowed for an adequate intake of food.

Three newborn infants with *localized areas of cyanosis* were observed by L. H. Smith (J. Pediat. 7:376 (Sept.) 1935). In 2 of the patients the cyanosis was limited to the face and in the third, cyanosis involved the upper thorax, the head, neck and arms. None of these

patients had asphyxia. Within 5 days the localized cyanosis disappeared entirely and the health of the infants was unimpaired. It was the opinion of the author that the cyanosis was the result of a partial obstruction of the venous circulation, possibly due to a vasomotor disturbance.

The tendency of *pemphigus neonatorum* to spread readily from one patient to another indicated to H. Carter and H. A. Osborn (Brit. M. J. 1:465 (Mar. 7) 1936) that the disease was caused by a microorganism. In pathologic sections,

the lesion was found to consist of an inflammatory involvement of the sub-epithelial tissues and various strains of staphylococcus aureus and staphylococcus citreus were isolated. The disease seemed to spread from some focus within a nursery and it occurred at the same time or immediately after the development of folliculitis in some of the patients, but the pemphigus was more severe because the deeper structures of the skin were involved. The best *treatment* for the disease was thought to be local applications of silver nitrate.

## PARASITIC DISEASES IN CHILDREN

By WALDO E. NELSON, A.B., M.D.

An attempt to determine the effect of *hookworm infestation* upon the health of school children has been made by A. E. Keller, J. T. Googe, H. B. Cottrell, D. G. Miller, Jr., and R. H. Harvey (J. A. M. A. 105:1670 (Nov. 23) 1935). The study was carried on in George County, Mississippi, where hookworm infestation is endemic. In a series of 1083 children, it was found that 79.5 per cent. were infested. Of these 187, or 17.3 per cent., had moderate or heavy worm infestations. The instance of anemia and malnutrition was essentially the same in those children with light infestations and in the negative or control group (those with no infestation). Those children having the greatest number of worms had the greatest degree of anemia and malnutrition. Diseased tonsils and teeth were present in practically the same extent in both control and infested groups. The authors point out that hookworm control is to be considered as part of a well-balanced public health program. The removal of the hookworm alone will bring about only partial and temporary improvement. Treatment of the anemia and malnutrition and removal

of foci of infection should be carried out. Data regarding the dietary habits of the children studied indicated deficiencies that could be responsible for the malnutrition.

A review of the literature concerning *trichinosis*, especially in children, is presented by I. P. Sobel (Am. J. Dis. Child. 51:367 (Feb.) 1936). In addition, 8 sporadic cases of trichinosis in children are reported. Seven of these children recovered; the eighth patient, a girl of 4 years, with fulminating trichinosis, died after an illness of only 4 days. All of the children who recovered had edema of the eyes, fever, muscular pains and eosinophilia. There was no eosinophilia in the child who died. The possibility is suggested that the absence of eosinophilia is a bad prognostic sign.

The author points out that while the intradermal injection of *Trichinella* antigen is of value in making the *diagnosis*, it has certain disadvantages and cannot replace the biopsy in making a definite diagnosis. Thus, a positive reaction may be the result of a previous trichinous infection as well as of an active one. However, since the specificity of the re-

action seems to diminish over long periods of time, a reaction to a low dilution would be strong evidence in favor of an active infestation. One other disadvantage is that the reaction is not strictly specific in that *Trichuris* infection may give positive results. A negative reaction which becomes positive later in the illness is strong evidence that the

case at hand is one of trichinosis. In the examination of muscles removed by biopsy, the importance of the earlier changes in the muscles are emphasized. These are: (1) basophilic granular degeneration; (2) multiplication and swelling of the muscle nuclei; (3) basophilic halo formation; and (4) focal interstitial myositis.

## EPIDEMIC PAROTITIS—(*Mumps*)

By ROBERT A. LYON, A.B., A.M., M.D.

Within the past few years, evidence points to one of the filtrable viruses as the etiologic agent of mumps. This information, together with the knowledge of the frequency of involvement of the central nervous system in this disease, has led to speculation in regard to the true nature of the disease.

In the opinion of Lamache and Dutrey (Bull. et. mém. Soc. Méd. d. hôp. de Paris 51: 1770 (Dec. 30) 1935), the disease is a general systemic infection and the parotid swelling is only one of the symptoms. Different types of symptoms of the *nervous system* in association with mumps were observed. In one instance a polyneuritis developed 5 or 6 days before the onset of parotid swelling. In the second patient a polyneuritis occurred 10 days before the onset of parotitis and shortly after the parotid glands had become swollen, there developed an orchitis, a quadraparesis and a bilateral involvement of the facial nerves. Only 8 to 10 cells were noted in the cerebrospinal fluids of these patients. In the third instance severe pain in the arms and later in the neck and shoulders preceded an attack of mumps by about 4 days. In the fourth instance a meningo-encephalitis occurred in a child 7 years of age on the second day of an attack of mumps. It was thought likely that the dissemination of the disease is quite

general throughout the body and it is probable that nervous tissue is especially susceptible.

The frequency of involvement of the *nervous system* has also been emphasized by O. Bäumlér (Monatschr. f. Kinderh. 63: 377, 1935). In his opinion this type of complication is more common than orchitis. The author has observed about 50 patients with meningeal or encephalitic symptoms occurring before, during, and after the appearance of the parotitis. Jaundice was another symptom seen in a few patients with mumps. The abdominal pain often occurring in patients was thought to be due to a hepatitis rather than to a pancreatitis.

Further evidence of the widespread effect of invasion of the virus of epidemic parotitis was an unusual type of *eye involvement* following mumps, which occurred in a patient 2 years of age, observed by W. Mikulowski (*Ibid.* 64: 101 (Dec. 2) 1935). Following a definite exposure to the disease, the child developed a swelling of the submaxillary glands and 3 days later the uvea, choroid, and the entire left eye became inflamed. During the next week there were *meningeal symptoms* and a *hyperglycemia*. The mumps virus was thought to be the etiologic agent causing inflammation of the eye, the brain and the pancreas, in addition to the salivary glands.

## POISONING IN CHILDREN

By WALDO E. NELSON, A.B., M.D.

**General Treatment.**—In an article on the prognosis of acute poisoning, H. L. Marriott (Lancet 1:795 (Apr. 4) 1936) states that the prognosis varies inversely with the delay in beginning treatment and that if the patient is seen within an hour or two, the thoroughness with which the stomach is washed out is the chief factor. Two gallons of water should be used, a pint at a time being run into the stomach. He stresses the importance of placing the patient in the proper position, *i. e.*, with the mouth and pharynx on a lower level than the larynx and trachea, so that fluid regurgitated around the stomach tube does not enter the air passages. The patient is placed in the prone position with the head extending over the end of the table and with the face directed towards the floor and supported by an assistant. The operator sits or kneels on the floor while passing the tube. The only swallowed poisons for which *gastric lavage is contraindicated* are the *corrosive acids and alkalis*.

The author states that there are only 5 common mechanisms by which life is primarily endangered in acute poisoning: (1) asphyxia; (2) depression of the central nervous system, *i. e.*, coma; (3) excitation of the nervous system, *i. e.*, violent delirium or convulsions; (4) dehydration and dechloridation; and (5) pain and shock. *Asphyxia* is effectively treated by clearing the patient's air passages by **artificial respiration** and by the administration of **oxygen** or of **oxygen and carbon dioxide**. *Coma* is not so easily controlled but fortunately its seriousness is often associated with asphyxia from respiratory obstruction or depression. The administration of **strychnine** and **coramine** in large doses repeated as often as once every hour is helpful in deep coma, so also is re-

peated lumbar puncture. *Dehydration* and loss of chlorides from vomiting and diarrhea are best controlled by **continuous intravenous saline therapy**. **Morphine** should be administered for *pain* and *shock* and the **barbiturates** for *delirium* and *convulsions*.

In view of the importance of accidental poisoning in children, the following abstract is given in some detail from an excellent article by A. O. Gettler and A. V. St. George (Am. J. Clin. Path. 5:466 (Nov.) 1935):

Among the sources of poisoning are the *silver polishes* containing cyanide salts; various dry *cleaning fluids* composed of carbon tetrachloride, trichloroethylene, pentachlorethane, propylene chloride, gasoline containing tetra-ethyl lead, benzene, and other solvents; many *deodorants*, *germicides* and *antiseptics* containing carbolic acid, lysol, cresol, bleaching powder, potassium chlorate, bichloride of mercury, iodine, boric acid, oxalic acid, and sodium carbonate (washing soda); *insecticides* and poisons for rodents in the form of powder, solution or paste and containing strychnine, Paris green, phosphorus, white arsenic or sodium fluoride; *ordinary household drugs* especially sugar-coated cathartic pills containing phenolphthalein, strychnine or atropine in some form; *shoe polish* or *shoe dyes* containing benzene or nitrobenzene; carbon monoxide from *leaking gaspipes or stoves* or from exhausts of motor cars; fumes from *freshly varnished and nonventilated rooms* due to the evaporation of turpentine or wood alcohol from the varnish; lead-containing *paint on toys, bedsteads* and other furniture and ethyl (grain) alcohol and whiskey.

**BORIC ACID POISONING.**—Chronic boric acid poisoning may occur in infants



from unwashed nipples that have been kept in boric acid, or from an old custom of giving babies cloths to suck which have been saturated in boric acid. The continued use of borated glycerin suppositories has also led to chronic poisoning. Acute boric acid poisoning is not common, but has occurred when boric acid solution has been injected subcutaneously by mistake instead of a physiologic saline solution.

*Symptoms* of acute poisoning are salivation, vomiting, diarrhea, bloody urine and delirium. The skin is cyanotic, cold and clammy. The symptoms in chronic cases are similar but much milder. They are usually anorexia, fretfulness and apparently considerable abdominal pain. There may be an irritating dermatitis as well as frequent periods of hematuria.

When the boric acid or borax has been swallowed, *treatments* should be directed toward the removal of the poison by **gastric lavage** and **colonic irrigation**, and toward the acceleration of excretion by giving **fluids**, chiefly in the form of **alkaline drinks**, and by **intravenous calcium gluconate** administration. Supportive measures to combat collapse must be instituted. In order to avoid errors, hospitals should color their boric acid with eosin or some other nontoxic dye.

**SODIUM CARBONATE (WASHING SODA) POISONING.**—The *symptoms* of sodium carbonate poisoning are vomiting, diarrhea, tetanic contractions, collapse and coma.

The *treatment* consists of **gastric lavage** and the administration of large amounts of **fluids containing lemon or grape fruit juice or dilute (1 to 4) vinegar**. Subcutaneous infusion of 5 per cent. **glucose** or **saline** may be given. *Alkalosis* should be combated with **sodium acid phosphate** and such stimulants as **strychnine** and **digitalis**

should be given by subcutaneous injection for *collapse*.

**POTASSIUM CHLORATE POISONING.**—In a reported fatal case of potassium chlorate poisoning, the *symptoms* were vomiting, diarrhea, clammy skin, dyspnea, cardiac weakness and a gradual change of the skin to a pale bluish-green, especially pronounced on the lips, nose and forehead. Icterus and a nephrosis with oliguria have been noted in some cases of chlorate poisoning.

*Treatment.*—Immediate **gastric lavage** and administration of copious amounts of **fluids** are indicated. **Stimulating treatment** for the heart and kidneys should be instituted. **Transfusions of blood** are of value.

**ARSENIC POISONING.**—Acute arsenic poisoning in children usually results from careless administration or from accidental ingestion of the drug. Chronic arsenic poisoning may result from its prolonged administration or from prolonged ingestion of food, such as vegetables sprayed with arsenic.

In the *acute* cases the *symptoms* may begin shortly after ingestion or within 2 or 3 hours. This is dependent upon the form of arsenic taken, its concentration, and whether or not a quantity of food is in the stomach. Symptoms usually consist of severe epigastric pain and vomiting, which is rapidly followed by a burning sensation in the mouth and esophagus and by profuse bloody diarrhea, so that dehydration and symptoms of collapse ensue. Convulsions in young children generally occur early, but coma, as a rule, is a late manifestation. It is thought to be due usually to paralysis of the muscles of respiration and circulation.

The *symptoms of chronic poisoning* are chiefly dependent upon disturbances in the nervous system. The most pronounced symptoms are an irritating eczematous eruption, frequently on the

extremities; brownish pigmentation of the skin, especially in the groins and the folds of the thighs; and a sensory neuritis, resulting in pains in the extremities, and, at times, in ataxia. Other neurological disturbances that may occur are disturbances in vision, hearing and taste, headache, giddiness, muscular tremors and loss of reflexes. Vasomotor disturbances may also occur.

*Treatment.*—In the *acute* cases treatment must be directed toward elimination of the arsenic by repeated **gastric lavage**, and administration of the **arsenic antidote** (either fresh **colloidal ferric hydroxide** made by adding an excess of an aqueous suspension of magnesium oxide to a solution of ferric sulphate, or a mixture of equal parts of **magnesium oxide** and finely divided medicinal **charcoal** suspended in water) given repeatedly in abundant amounts. **Colonic irrigation, saline and glucose solution** should be given intravenously and subcutaneously. **Blood transfusions** should also be given. If there are symptoms of *collapse* or *cardiac* or *respiratory failure*, **supportive drugs** must be employed.

In the case of *chronic poisoning*, efforts must be directed toward the determination of the source of the poisoning and its elimination. Efforts should be made to eliminate the arsenic from the system by giving the child an **acid residue diet**, in which milk is included, and also intravenous injections of **sodium thiosulphate**. The general health must be built up by adequate **dietary measures**.

**PHOSPHORUS POISONING.**—*Acute* phosphorus poisoning may be divided into 3 stages: (1) acute gastroenteric symptoms; (2) quiescent stage, lasting a day or two; (3) symptoms similar to an acute yellow atrophy of the liver. *Treatment* is generally of little avail, since the symptoms do not occur until a

good deal of the poison has been absorbed and has exerted its deleterious action. Large amounts of **liquid petrolatum** should be **administered and then removed by siphonage with the stomach tube**. Repeated **lavages** of a 1 per cent. solution of **potassium permanganate** should next be instituted and, finally, suspensions of finely divided medicinal **charcoal** in large amounts should be given. **Morphine** or **barbiturates** should be given liberally in case of great pain.

**ANILINE AND NITROBENZENE POISONING.**—Aniline poisoning results in the production of methemoglobin from hemolysis of erythrocytes. The principal symptoms are fatigue, nausea, headache, giddiness, tinnitus aurum, skin irritation and sleepiness. There may be paralysis, abdominal cramps, absence of reflexes, unconsciousness, palpitation and dyspnea. There is an anemic pallor and cyanosis, and the eyes may be icteric. The peculiar discoloration of the skin is almost diagnostic. The urine contains methemoglobin, hemoglobin, porphyrin, bilirubin, albumin and casts.

*Treatment.*—The **source** of the poison should be **removed** at once. If it is on the **skin**, it should be **washed off with soap and water**; if taken by **mouth**, the **stomach** should be **washed out** and a suspension of medicinal **charcoal** in **water and magnesium sulphate** given in liberal amounts. **Caffeine, oxygen, and saline infusions** are usually indicated and **artificial respiration** may be necessary. **Blood transfusions** are invaluable and should be given promptly. The resulting anemia should be subsequently treated.

**BENZENE POISONING.**—Benzene poisoning may be either acute or chronic. The *acute* type begins with a state of inebriation in which gaiety, excitement and increased self confidence precede a state of giddiness, uncertain gait, sleepi-

ness, nausea, vomiting, headache and facial pallor. The skin later assumes a greyish, blue tint, and there are cyanosis of the extremities, muscular spasms, blowing respiration, fall in temperature and blood-pressure, and, finally, muscular paralysis, convulsions, deep coma and death. A frequent complaint is burning sensation in the throat and eyes.

*Chronic* benzene poisoning usually results from prolonged inhalation of the poison or ingestion of small amounts in liquids as in denatured alcohol, etc. Fine punctate hemorrhages may be scattered over the entire body and on the surfaces of the mucous membrane. There is anorexia and nausea, and headaches are quite frequent. Such neurological symptoms as tremors, faltering gait, fatigue, giddiness and abdominal cramps and pains, insomnia and cardiac palpitations are common. The urine generally contains small amounts of albumin and granular casts. In the cases ending fatally, a generalized sepsis, due to infection of the hemorrhagic foci, is frequently found. Early in the illness there is a slight or moderate leukocytosis. However, this is quickly followed by a leukopenia with a relative lymphocytosis and anemia. This leukopenia is due to the effect of the benzene on the bone-marrow.

*Treatment.*—In both the acute and chronic types of cases the sources of benzene must be eliminated. In the *acute* case, if the patient is unconscious, **artificial respiration** or the use of the **respirator** with **oxygen and carbon dioxide** administration should be employed. **Stimulants** for the heart and respiration should also be given. If the benzene has been taken by *mouth*, a **suspension (3 per cent.) of medicinal charcoal and water** should be used as a **lavage**. This should be followed by the liberal administration of a **suspension of medicinal charcoal in mag-**

**nesium sulphate solution.** If the poisoning has resulted from *inhalation*, attempts have been made to bind the benzene by the intravenous injection of 5 c.c. (1½ drams) of a 10 per cent. **lecithin emulsion.** Its use, however, is of doubtful value.

In *chronic* poisoning measures directed toward combating the anemia and overcoming the injury to the bone-marrow must be employed. This is accomplished chiefly with **transfusions**, **daily injections of liver extracts**, and other **blood builders** and by proper diet.

**STRYCHNINE POISONING.**—The *symptoms* of strychnine poisoning are agitation and muscular twitching, which is followed by cyanosis, intermittent respirations and convulsions.

Reference is made to the successful *treatment* of a severe case of strychnine poisoning by Stahlberg and Davis by the injection of **sodium amytal** intravenously and **tribrom-ethanol** in water by rectum. **Gastric lavage** with a suspension of **medicinal charcoal and tannic acid** should be given at once. **Chloral hydrate** as well as **ether** or **chloroform** may be given for the spasms. An intravenous injection of **pernokton** may be given in drop doses.

**BISMUTH SUBNITRATE POISONING.**—An instance of bismuth subnitrate poisoning in an infant 7 weeks of age is reported by H. N. Runsdorf and A. Nightingale (J. Pediat. 8:624 (May) 1936). The drug had been prescribed for treatment of diarrhea. The mother had been instructed to give "as much as could be placed on the tip of a teaspoon to be given with each feeding and if the symptoms did not abate, the amount was to be gradually increased." The dosage was increased until almost 1 teaspoonful was given with each feeding. The child's skin became increasingly cyanotic, and it was noted that he would writhe and scream soon after eating. Except for

the cyanosis and the peculiar odor of the breath, there were no abnormal physical findings. The laboratory findings were negative, except that the urine showed an abnormal amount of nitrites. It has been shown that subnitrate of bismuth

is capable, under the influence of certain bacteria in the intestines, of giving off nitric acid and nitrites, and that the symptoms of poisoning are due to the latter. The effect is upon the hemoglobin with formation of methemoglobin.

## POLIOMYELITIS

By FRANK E. STEVENSON, A.B., A.M., M.D.

**Etiology.**—(A) **PREDISPOSING CAUSES.**—1. *Climate.*—Historically, the first good account of epidemics of poliomyelitis proceeds from western Europe, according to E. B. Shaw (Northwest Med. 35:39 (Feb.) 1936). During the early part of the present century, the disease secured a foothold on the eastern seaboard of this country, spreading about New York and up the New England States, where epidemics have periodically recurred ever since. The disease spread westward over the northern portion of the United States.

Definite epidemics began on the west coast approximately in the year 1910, and from this original focus in northern California, the disease has spread in extent and increased in severity. The southernmost portion has been most involved. However, the author states that there is every reason to believe that there will be an increase in the disease in the Pacific Northwest. With the exception of the Pacific coast, the disease showed little tendency to spread southward until 1935, when epidemics were reported in North Carolina by C. V. Reynolds and J. C. Knox (Am. J. Pub. Health 26:95 (Feb.) 1936); in Virginia by I. C. Riggin (*Ibid.* 26:98 (Feb.) 1936) and W. W. Waddell, Jr., and C. W. Purcell (*Ibid.* 26:104 (Feb.) 1936); in Kentucky by A. T. McCormack and F. W. Caudill (*Ibid.* 26:101 (Feb.) 1936) and H. R. Leavell (Kentucky M. J. 34:110 (Mar.) 1936); in Tennessee by W. C.

Williams (Am. J. Pub. Health 26:103 (Feb. 1936). The disease may occur in the tropics; S. M. Lambert (J. Trop. Med. 39:41 (Feb. 15) 1936) reported an epidemic occurring in Samoa in 1933.

2. *Age.*—In the group of patients studied by Williams (*loc. cit.*) and by Riggin (*loc. cit.*), 62 per cent. and 59.7 per cent., respectively, were in the first 10 years of life. E. J. Barnett and C. L. Lyon (Northwest Med. 34:429 (Nov.) 1935) found that 70 per cent. of their cases occurred in children between the ages of 5 and 10 years. R. W. Meals, V. F. Hauser and A. G. Bower (California and West Med. 43:123 (Aug.); 215 (Sept.) 1935) observed an increase in the number of patients in the late second and in the third and fourth decades of life; however, 63 per cent. of their patients were in the first 15 years of life.

3. *Sex.*—Poliomyelitis occurs more frequently in the male than in the female. Fifty-four per cent. of the patients of Reynolds and Knox (*loc. cit.*) and 57 per cent. and 55.5 per cent. of the patients reported by McCormack and Caudill (*loc. cit.*) and Leavell (*loc. cit.*), respectively were of the male sex. G. deN. Hough, Jr. (Surg. Gynec. and Obst. 61:90 (July) 1935) observed a ratio of 3 to 2 in favor of the male patients and E. J. Barnett and C. L. Lyon (*loc. cit.*), a ratio of 3 to 1.

4. *Season.*—Poliomyelitis is primarily a warm weather disease. According to

TABLE I

|  | Age in Years          | 0-4 | 5-9 | 10-14 | 15-19 | 20-24 | 25-34 | 35-44 | 45 and over |
|--|-----------------------|-----|-----|-------|-------|-------|-------|-------|-------------|
| Reynolds and Knox ( <i>loc. cit.</i> )     | Per cent. of Patients | 51  | 27  | 9     | 5     | 2     | 3     | 3     |             |
| McCormack and Caudill ( <i>loc. cit.</i> ) | Per cent. of Patients | 44  | 28  | 16    | 7     | 5     |       |       |             |
| J. C. Wilson and P. J. Walker*             | Per cent. of Patients | 42  |     | 30    |       | 26    |       |       | 2           |

\*Arch. Int. Med. 57:477, Mar., 1936.

TABLE II  
(Waddell and Purcell (*loc. cit.*)  
*Age Groups*

|                         |    |                     |    |
|-------------------------|----|---------------------|----|
| Youngest—8 weeks        |    | 7 to 8 years.....   | 6  |
| Under 6 months.....     | 5  | 8 to 9 years.....   | 7  |
| 6 months to 1 year..... | 3  | 9 to 10 years.....  | 3  |
| 1 to 2 years.....       | 6  | 10 to 11 years..... | 5  |
| 2 to 3 years.....       | 13 | 11 to 12 years..... | 3  |
| 3 to 4 years.....       | 3  | 12 to 15 years..... | 12 |
| 4 to 5 years.....       | 6  | 16 to 20 years..... | 9  |
| 5 to 6 years.....       | 8  | 21 to 25 years..... | 12 |
| 6 to 7 years.....       | 5  | 26 to 30 years..... | 4  |
|                         |    | 31 to 35 years..... | 1  |

McCormack and Caudill (*loc. cit.*), 308 cases of the disease occurred in Kentucky in 1935 between June 1 and November 1; the epidemic reached its peak in August, as did the 1934 epidemic in Spokane, recorded by E. J. Barnett and C. L. Lyon (*loc. cit.*). In Virginia, in the same year, the greatest number of cases was reported during the middle of July (Riggin).

From a review of the records of poliomyelitis occurring in North Carolina during the past 10 years, Reynolds and Knox (*loc. cit.*) report that August was the month of greatest incidence. However, during the 1935 epidemic, the peak incidence was reached during the month of June.

5. *Race*.—According to P. H. Harmon (*J. Infect. Dis.* 58:331 (May-June) 1936), the incidence of poliomyelitis in both southern and northern local-

ities is from 2 to 4 times that in negroes. Mortality rates per 100,000 of population are practically identical. However, the case fatality rates among negroes exceed those of the white race. The author states that it is possible that opportunity for contact infection is the determining factor.

In a group of 308 cases reported by McCormack and Caudill, 91 per cent. were of the white race and 9 per cent. were negroes. During the epidemic reported by Reynolds and Knox in North Carolina, 77 per cent. were white, 14 per cent. were negroes, 2 per cent. were Indians, while the race of 4 per cent. was unknown. The attack rate per 100,000 among whites was 21.48, among negroes 13.50, among Indians 84. The population of North Carolina is 70 per cent. white, 29.5 per cent. negroes, 0.5 per cent. Indian. Of the group of pa-

tients reported by Leavell (*loc. cit.*), 79.9 per cent. were of the white race and 20.1 per cent. were negroes. A considerably larger number of negroes contracted the disease than would be anticipated, in view of the fact that the negro population in the community was approximately 15 per cent. of the total population.

6. *Tonsillectomy*.—In Spokane, in previous years so many cases of the bulbar type of poliomyelitis followed tonsillectomy, that it could not be considered merely a coincidence. However, in 1934, while there was a large number of patients with the bulbar form, E. J. Barnett and C. L. Lyon (*loc. cit.*) failed to observe a case in which a child had had a recent tonsillectomy. According to H. R. Leavell (*loc. cit.*), the presence or absence of tonsils seems to be of little significance as a predisposing factor to poliomyelitis.

7. *Blood Group*.—T. Madsen, E. T. Engle, C. Jensen and I. Frenchen (J. Immunol. 30:213 (Mar.) 1936) collected 1118 cases in the 1934 epidemic of poliomyelitis in Denmark, in which the blood group of the patient was determined. The authors found no evidence of special susceptibility or resistance which could be related to the blood group.

8. *Economic Status*.—In the group of patients observed by Leavell (*loc. cit.*), the economic status was recorded as excellent or good in 12.6 per cent. of the families, fair in 19.3 per cent., and poor in 61.4 per cent. In 6.7 per cent. of the patients, satisfactory information was not obtained.

9. *Rural vs. Urban Districts*.—Reynolds and Knox (*loc. cit.*) found that 65 per cent. of their patients were from the rural districts.

10. *Swimming*.—Meals, Hauser and Bower (*loc. cit.*) state that the voluntary history of illness following swimming,

particularly in hypertonic ocean water, was most striking in the patients under their observation. The presence of the virus in the water is questionable, but the increasing of contacts, the washing of protective mucus from the nose and throat, and the vascular changes in the nasopharynx incident to chilling, were thought to be important factors. However, Leavell (*loc. cit.*) found that 70.6 per cent. of his patients did not go swimming; 20.2 per cent. went swimming (presumably not in ocean water); while 9.2 per cent. were infants.

11. *Miscellaneous Factors*.—The *occupation* of the patient or parents, *previous illness*, *complexion* and other *physical characteristics*, *dietary* and other habits, *sanitation* of the home, the presence of *insects*, *rodents* and other *animals*, *visits* to gatherings, absence from the city, and a host of other items seem to be of little or no significance in the etiology of poliomyelitis, according to the studies of Leavell (*loc. cit.*).

(B) SPECIFIC CAUSES.—1. *Globoid Bodies*.—Since the causative agent of poliomyelitis is definitely regarded as a filter-passing virus, G. A. Logrip (J. Bact. 31:245 (Mar.) 1936) attempted to determine the nature of the globoid bodies, which were first reported in 1913. The author found that the opalescence reported in the poliomyelitis virus culture as well as the micrococcoid forms can be produced in the absence of the virus. The establishment of an electric field will cause tissue lipoids to pass into suspension and react to stains similar to the "globoid body" forms.

2. *Virus—Culture*.—A. B. Sabin and P. K. Olitsky (Proc. Soc. Exper. Biol. and Med. 34:357 (Apr.) 1936) used media prepared from the brain and cord, lungs, kidneys, liver and spleen of human embryos for culture media. Propagation of the virus in human embryonic nervous tissue as contrasted with

the complete lack of growth in the other tissues emphasized the limited affinity of the poliomyelitis virus. According to the authors, multiplication of the virus can occur in cultures prepared with tissues preserved in the refrigerator for at least a week.

According to F. Eberson (Science 83: 324 (Apr. 3) 1936), it is stated generally, and it is sometimes accepted as a fact, that filtrable viruses cannot be cultured on ordinary lifeless media. In his early studies, the virus was grown on macerated sheep brain which the author considered to be a lifeless culture medium. In the recent review of this work he contends that the statement that the brain tissue medium was lifeless because of the mode of sterilization, was erroneous.

*Susceptibility of Experimental Animals.*—J. A. Toomey and K. R. Phelps (Proc. Soc. Exper. Biol. and Med. 33: 624 (Jan.) 1936) confirmed the work of W. J. Nungester (*Ibid.* 30:1128 (May) 1933) that mucin added to poliomyelitis virus may accentuate its potency when injected into the *mouse*. However, the mouse cannot be used for experimental studies, because inconstant results are obtained and the pathological sections are not definitely typical.

The *spider monkey* (*Ateles Ater*), like other new world varieties, is naturally refractory to experimental inoculation with the poliomyelitis virus (monkey passage), according to E. M. MacKay and C. R. Schroeder (Proc. Soc. Exper. Biol. and Med. 33: 373 (Dec.) 1935).

*Strains.*—From a study of the 1934 epidemic of poliomyelitis in Los Angeles, Meals, Hauser and Bower (*loc. cit.*) suggest that there is more than one strain of human poliomyelitis virus. The most important evidence offered in support of this conclusion was the very unusual clinical picture observed during the epidemic; the high incidence of the

disease among adults, particularly doctors and nurses; and the appearance of mild symptoms in a few patients who had had poliomyelitis.

*Transmission.*—CONTACT.—F. Arden (M. J. Australia 2:283 (Sept. 21) 1935) reported poliomyelitis in 3 siblings in a well isolated home where the apparent source of the infection was a traveler who, while ill, had remained in the home. In Leavell's group of patients only 0.8 per cent. apparently contracted the disease through *direct* contact, while 5.9 per cent. were exposed by *indirect* contact. In 90.8 per cent. of his patients there was no known contact.

MILK-BORNE.—According to a study made by Leavell (*loc. cit.*), Dairy A supplied only 27.33 per cent. of the milk, yet 42.9 per cent. of his patients with poliomyelitis obtained milk from this source. The author points out that approximately 65 per cent. of Dairy A's milk is sold through chain stores and the corner grocery—stores patronized by the lower economic group. According to the author, there was no definite evidence that the disease was milk-borne.

WATER.—In the group of patients reported by Leavell (*loc. cit.*), 70.6 per cent. used city water only; 20.2 per cent. used city and other water supplies; 2.5 obtained water from sources other than the city. Apparently there was no evidence of water transmission.

PRIVIES.—In 56.3 per cent. of Leavell's patients, privies were within 150 feet from the dwelling. There was approximately one case of poliomyelitis to every 100 privies. According to the author, this finding may indicate only that the greater number of cases occurred in the more crowded and poorer sections.

INSECTS AND RODENTS.—H. Wennerberg (Brit. J. Child. Dis. 32: 163 (July-Sept.) 1935) contends that the disease is transmitted by *mosquitoes*. A history

of the presence of mosquitoes was obtained by Leavell (*loc. cit.*) in 91 per cent. of his patients, stable flies in 90 per cent., and *rats* and *mice* in 83 per cent.

**RAW FRUITS AND VEGETABLES.** — A history of ingestion of raw fruits and vegetables was obtained in all but 3 of Leavell's patients.

**SWIMMING.** — No contact through pools could be obtained in Leavell's (*loc. cit.*) group, consisting of 20.2 per cent. of the patients who went swimming.

**Portal of Entry.** — **GASTROINTESTINAL TRACT.** — Meals, Hauser and Bower (*loc. cit.*) found that approximately 16 per cent. of their patients had suffered a preceding enterocolitis, often with mild encephalitic symptoms. These findings suggest the possibility of a primary intestinal infection with neurological complications, or a possible gastrointestinal tract atrium of the poliomyelitis virus.

According to J. A. Toomey (Am. J. Dis. Child. 50:1362 (Dec.) 1935), clinical observations indicate that the virus of poliomyelitis may spread up the vagus nerve from the gastrointestinal tract to involve the vagal nucleus and, by continuity, extend to other tissues. The production of isolated paralysis of the muscles of the facial nerve, according to Toomey (*Ibid.* 51:58 (Jan.) 1936), may best be explained by assuming that the portal of entry was the gastrointestinal tract. The author has been able to produce paralysis of this type by way of the gustatory fibers as well as through the chorda tympani.

In experimental poliomyelitis, J. A. Toomey (Science 82:200 (Aug. 30) 1935) states that 2 factors combine and the combination material destroys motor cells. One of these factors is *monkey cord virus* and the other is the *toxic material produced in the intestinal tract*. In the human being, the causative agent

usually enters the digestive tract ready-made. According to the author, all the vagaries of the disease, even the reason why the lumbar region seems to be the first involved, are easily understood in the light of the theory that the virus enters through the gastrointestinal tract.

H. K. Faber (*Ibid.* 82:42 (July 12) 1935) contends that the gastrointestinal tract cannot be accepted as the portal of entry on the basis of early or limited involvement of the lumbar cord. From animal experimentation with nasal inoculation in which the gastrointestinal tract could be ruled out with some degree of certainty as the portal of entry, the author observed that the lumbar cord was involved in more than half of the animals.

E. H. Lennette and N. P. Hudson (J. Infect. Dis. 58:10 (Jan.-Feb.) 1936) repeatedly instilled suspensions of virus containing cord of monkeys into loops of isolated bowel in 4 M. rhesus monkeys without producing infection. Subsequent attempts were preceded by washing out the loops with phosphate buffer solution in an attempt to increase the permeability of the intestinal mucosa. This method, which was found to be so useful by N. P. Hudson, E. H. Lennette and F. B. Gordon (J. A. M. A. 106:2037 (June 13) 1936) in increasing the incidence of infection by the nasal route, was ineffective when applied to the lower bowel, since evidence of infection failed to develop. S. Flexner (J. Exper. Med. 63:209 (Feb.) 1936) questions whether under rigid experimental conditions infection is ever secured by the way of the stomach and intestines.

**RESPIRATORY TRACT.** — S. Flexner (*Ibid.*) states that while the gastrointestinal source of infection is much disputed, the portal of entry through the intestinal tract is generally accepted. There is no difference of opinion on the greater ease and frequency with which



infection can be experimentally induced *via* the nasal passages or the virus detected in secretions from the passages.

**INTRAVENOUS ROUTE.**—C. Armstrong (Pub. Health Rep. 51:241 (Mar. 6) 1936) found that picric acid (see *Prophylactic Treatment*) instilled in the nose tends to protect monkeys from intravenous inoculation. Hudson, Lennette and Gordon (*loc. cit.*) determined that section of the olfactory nerves prevented infection after both intranasal and intravenous inoculation. The selectivity of the virus for the olfactory pathway to the central nervous system was indicated by recovery of the virus from the nasal passages following intravenous injection. According to Armstrong (*loc. cit.*), the infection following intravenous inoculation is due to the escape of the virus from the blood stream into the nasal membrane, from where it reaches the nervous system by way of the olfactory tract. However, Hudson, Lennette and Gordon (*loc. cit.*) observed that sublethal doses of the virus given intravenously were made fatally infectious by damage to the cerebral cortex from starch injections.

**CUTANEOUS.**—J. D. Trask and J. R. Paul (J. Bact. 31:527 (May) 1936) report a relatively high incidence of experimental poliomyelitis in monkeys following *intracutaneous* injections of comparatively small doses of the w. f. d. strain, a so-called human strain. Several cases of the disease in human beings have apparently followed the *subcutaneous* injections of poliomyelitis vaccine, according to J. P. Leake (Am. J. Pub. Health 26:148 (Feb.) 1936).

**Pathology.**—The cellular infiltration of the meninges present in certain encephalomeningitic processes, such as poliomyelitis, is essentially limited to one component, the pia (H. W. Williams: Arch. Path. 21:35 (Jan.) 1936). According to the author, this infiltra-

tion is secondary to the encephalitic process. In contrast, the seat of the inflammation in purulent meningitis is primarily the subarachnoid space, the pia evincing merely symptomatic inflammation.

The cases of poliomyelitis observed by Meals, Hauser and Bower (*loc. cit.*) were quite variable in their manifestations. The majority of the patients revealed some degree of initial toxemia, although in many cases there was an absence of the usual early neurological changes. A small number of the patients were afebrile during the entire period of observation.

A few patients did not complain of headache or painful oculomotion; many had sore throat without local evidence of inflammation. A large number of the patients suffered an initial diarrhea, often accompanied by abdominal pains, and occasionally by vomiting. Now and then mental dullness suggested cerebral involvement. A primary gastrointestinal infection often seemed to be present. Occasionally, the degree of abdominal pain, the distention, and vomiting were quite alarming.

According to J. M. Smellie (Practitioner 136:203 (Feb.) 1936), the outstanding physical sign is rigidity of the spinal muscles. This rigidity is, as a rule, most marked in the lower cervical and the upper dorsal region, and only slightly so in the upper cervical spine. Accordingly, the child is able to flex the head on the neck, but difficulty is often met with in attempting to flex the neck on the shoulders. The *chin sign* is often positive. This sign is elicited by instructing the patient to touch his sternum with the chin; if positive, the patient will open the mouth.

While less severe than in previous epidemics, nearly all of the patients observed by Meals complained of pain in the cervical or lumbar spine. Although stiffness of the neck and spine

## SYMPTOMATOLOGY

|                                     | Waddell and<br>Purcell<br>Per cent. | W.W. Nicholson<br>Per cent.<br>(Kentucky<br>M. J. 34:115<br>(Mar.) 1936) | Wilson and<br>Walker<br>Per cent. | Barnett and<br>Lyon<br>Per cent. |
|-------------------------------------|-------------------------------------|--|-----------------------------------|----------------------------------|
| Fever....                           |                                     | 90.0   |                                   | 100                              |
| Fever on examination....            | 54.0                                |  |                                   |                                  |
| Vomiting....                        |                                     | 50.0   | 44.0                              | Occasional                       |
| Nausea .....                        | 6.3                                 |  |                                   |                                  |
| Pain in abdomen.....                | 18.0                                |  |                                   | 4.3                              |
| Enlarged spleen.....                | 1.8                                 |  |                                   |                                  |
| Diarrhea.....                       | 9.0                                 | 1.0  |                                   |                                  |
| Constipation.....                   |                                     | 9.0  |                                   |                                  |
| Dysphagia.....                      | 0.9                                 |  | 1.0                               |                                  |
| Sore throat.....                    | 4.5                                 |  |                                   |                                  |
| Coryza.....                         | 1.8                                 | 24.0   | 9.0                               |                                  |
| Headache.....                       | 55.0                                | 76.0   | 49.0                              | Occasional                       |
| Dizziness.....                      | 1.8                                 |  |                                   |                                  |
| Listlessness and drowsiness..       | 15.3                                | 22.0   | 8.0                               |                                  |
| Excitement and restlessness...      |                                     |  |                                   | Common                           |
| Convulsions .....                   | 1.8                                 |  |                                   | 2.0                              |
| Tremor or twitchings .....          |                                     | 8.0  | 4.0                               | Common                           |
| Tenderness and pain.....            | 9.0                                 | 13.0   | 18.0                              |                                  |
| Pain and stiffness of neck and back | 37.9                                | 67.0   | 59.0                              | 97.7                             |
| Rigidity neck only .....            |                                     |  | 3.0                               |                                  |
| Rigidity back only .....            |                                     |  | 5.0                               |                                  |
| Muscle weakness .....               | 21.6                                |  | 20.0                              |                                  |
| Difficult respirations.....         | 2.7                                 |  | 2.0                               |                                  |
| Kernig's sign .....                 |                                     | 3.0  | 15.0                              |                                  |
| Brudzinski's sign .....             |                                     |  | 16.0                              |                                  |
| Bulging fontanel.....               |                                     | 1.0  |                                   |                                  |
| Retention of urine.....             | 1.8                                 |  |                                   |                                  |
| Arthritis .....                     |                                     |  | 34.0                              |                                  |
| Changes in reflex.....              | 47.8                                |  | 18.0                              | Common                           |

(\*Arch. Int. Med. 57:477 (Mar.) 1936).

was often absent, the *spine sign* was usually positive. The degree and duration of muscle pain, tenderness, and severe cramping were out of proportion to the motor phenomena. According to Smellie (*loc. cit.*), Kernig's sign is usually absent.

In the group of patients observed by Meals, Hauser and Bower (*loc. cit.*), the *reflexes* remained intact, although they were often diminished and frequently asymmetrical. *Muscle weakness* was often very mild or transient; pain on motion was sometimes pronounced.

Sensory phenomena seemed to be uniformly out of proportion to the motor changes. Occasionally, the hyperesthesia was localized contralateral to the paresis (Brown-Séquard's phenomena).

**Laboratory.**—**CEREBROSPINAL FLUID.**—The color of the fluid is usually either *clear* or slightly *opalescent* and the *pressure* is usually normal or slightly elevated, according to Shaw (*loc. cit.*), Nicholson (*loc. cit.*), Waddell and Purcell (*loc. cit.*). In 46 per cent. of the patients of Meals, Hauser and Bower (*loc. cit.*), the pressure was normal.

**CELLS.**—Nicholson (*loc. cit.*) observed the cell count to range between 10 and 500 per c.mm. Occasionally a count of 1500 cells was observed. According to Shaw (*loc. cit.*), the average count ranges between 200 and 300 cells. Waddell and Purcell obtained an average count of 155.4 per c.c. In 39 of their patients the count was less than 12 cells per c.mm. in 26 patients the count ranged between 20 and 60; in 13 the cells numbered between 60 and 100; in 12 between 100 and 200; while in 15 patients the cell count was above 200 per c.c. The highest count was 1480. The cell count was repeated on 8 of the 39 patients who had no increase in cell count upon admission; 3 were then found to have a cellular increase. According to Shaw, the cell count in bulbar

cases with little cord involvement is usually low, ranging from 50 to 100 cells per cm.

**DIFFERENTIAL COUNT.**—Meals, Hauser and Bower (*loc. cit.*) observed that the cells, when increased, were predominately lymphocytes. In 41 of the patients of Waddell and Purcell, the type of cell was the lymphocyte. In 47 of the patients the polymorphonuclear leukocytes predominated, while in 3 instances the cells were equally divided. Nicholson (*loc. cit.*) states that the type of cell depends largely upon the stage of the illness. During the early stage the polymorphonuclear leukocytes may be increased, while later the lymphocytes may predominate.

**PROTEIN.**—Shaw found the globulin rather constantly increased. In 39 of the cases observed by Waddell and Purcell, an increase in protein was the only spinal fluid finding indicative of the disease; 6 of these patients later were found to have the typical cellular reaction. Meals, Hauser and Bower obtained negative spinal fluid findings in 33 per cent. of their patients.

**SUGAR.**—In a group of 69 children, Waddell and Purcell obtained an average sugar content of 59 mg. per 100 c.c.

**CHLORIDES.**—The average chloride content of the spinal fluid obtained on the spinal fluid by Waddell and Purcell on a group of 50 patients was 584 mg. per 100 c.c.

**COLLOIDAL-BENZOIN AND COLLOIDAL GOLD TEST.**—Meals, Hauser and Bower have concluded that the presence of a positive colloidal-benzoin test or colloidal gold test without other spinal fluid changes or neurologic findings is not significant or conclusive.

**BLOOD.**—The white blood cell count, according to Shaw (*loc. cit.*), varies considerably; usually the total count is normal, with a relative increase in the polymorphonuclear leukocytes. Accord-

ing to P. Plum (Ugesk. f. laeger 97: 1012 (Oct. 3) 1935), the neutrophil leukocytosis is more marked in grave than in mild cases, with a slight shift of the hemogram to the left. In respiratory paralysis it is stated that a relatively greater number of polymorphonuclear leukocytes appear immediately before the onset of the paralysis, with a slight shift to the left and with a moderate increase in the absolute number of leukocytes. Similar changes were observed in 3 patients with the bulbar form of the disease.

**BLOOD SUGAR.**—Determination of blood sugar in monkeys, according to C. W. Jungeblut and R. Resnick (Am. J. Dis. Child. 51:91 (Jan.) 1936), reveal no significant deviation from the level observed in normal monkeys. However, in some paralyzed animals there occurs an ante mortem rise.

Dextrose *tolerance* tests in poliomyelitic monkeys demonstrate a functional inability to eliminate a test dose of sugar from the circulatory system in the same length of time as do normal monkeys. This derangement appears to be unrelated to either the duration or the extent of the paralysis. However, in contrast with the effect of the diphtheria toxin, poliomyelitic monkeys respond to the blood sugar lowering effect of insulin as well as do normal monkeys.

**Types.**—**BULBAR.**—In a group of 431 patients with poliomyelitis reported by J. A. Toomey (*Ibid.* 50:1362 (Dec.) 1935), 68 had the bulbar form of the disease. The latter group was divided into 2 groups: Group 1 consisted of 45 patients who had symptoms referable to the vagus nerve first, and only later had involvement of the other cranial nerves; 26 of these patients died. Group 2 consisted of 23 patients who had a primary involvement of the seventh nerve, and only occasionally showed extension to the other nerves of the bulb.

Strictly speaking, it is incorrect to classify all cases with respiratory paralysis as belonging to the bulbar type. The majority of respiratory symptoms, according to E. B. Shaw (Northwest. Med. 35:39 (Feb.) 1936), are due to involvement of the intercostal muscles of the diaphragm and result from lesions in the cord. True bulbar respiratory involvement commonly accompanies paralysis of the pharynx, the tongue and the larynx. Respiration in these cases is usually accompanied by hiccough and bizarre variations in respiratory rhythm. Death is due as much to accompanying vasomotor paralysis as to paralysis of respiration.

**MENINGEAL TYPE.**—M. Jaccottet and C. Rivier (Arch. de méd. d. enf. 37:393 (July) 1934) have reported 5 cases of the meningitic type of poliomyelitis.

**POLIOENCEPHALITIS.**—According to Shaw (*loc. cit.*), the term polioencephalitis can seldom if ever be used with accuracy. Actual lesions of the fore brain are rarely demonstrable.

**ABORTIVE.**—According to W. Keller (Deutsche med. Wchnschr. 61:1922 (Nov. 29) 1935), it has been shown that 800 to 900 abortive cases occur for every 100 cases with typical paralysis.

**Complications and Sequelæ.**—G. deN. Hough, Jr., (Surg., Gynec. and Obst. 61:90 (July) 1935) states that hip flexion deformity, which is a combination of flexion and abduction, is a disabling and common complication. It occurred in 19 per cent. of 622 cases seen at the orthopedic clinic.

In the group of cases reported by Meals, Hauser and Bower (*loc. cit.*), sequelæ of a psychasthenic or neurasthenic nature were more common than previously observed. Insomnia and nightmares were occasional complaints. Some of the patients were irritable and emotionally unstable. Others complained of mental fatigability.

Symptoms of neurocirculatory asthenia were not uncommon, characterized by symptoms of sudden weakness, vertigo, palpitation and breathlessness; occasionally, localized edema was present.

Trophic disturbances were observed, such as excessive growth of the finger nails of one hand with retardation on the other, hypertrichosis of the legs only, loss of pigmentation of the hair of one involved extremity, herpes, and the like. These changes were thought to be due to primary involvement of the sympathetic nervous system.

**ATELECTASIS.**—M. B. Brahdy and M. Lenarsky (J. Pediat. 8:420 (Apr.) 1936) observed at least 7 cases of massive atelectasis in a group of 27 patients who survived the original respiratory paralysis. The authors point out that this complication clinically is often confused with pneumonia. Massive atelectasis is said to be the result of a prolonged occlusion of the lumen of a large bronchi. Intercurrent respiratory infections, which increase the secretion of mucus, and an ineffectual cough are predisposing factors.

**Multiple Cases.**—According to the study of Barnett and Lyon (*loc. cit.*), although a total of 61 children came into direct contact with active cases observed by the authors, none developed the disease. However, 2 children were suspected of having contracted a mild, abortive form of poliomyelitis.

**Relapse and Second Attack.**—L. Cohen (New England J. Med. 213:601 (Sept. 26) 1935) recognizes 2 groups of recurrent poliomyelitis which are definitely distinct from each other. One group, which is not a reinfection, is due to recrudescence of the infection and occurs within 4 months of the first attack. The second and much less common group, a true reinfection, makes its appearance 2 or more years after the first attack. Two cases of second attacks

of poliomyelitis were observed, thus increasing the number of reported cases of this type to 15.

Meals, Hauser and Bower (*loc. cit.*) found that some of their patients suffered repeated attacks. Two patients, after an apparent recovery from a bulbar infection, suddenly died with further extension of the medullary involvement.

**Immunity.**—Cohen (*loc. cit.*) states that although one attack of poliomyelitis produces a permanent immunity in monkeys, immunity derived from an attack in the human being is absolute only for a period of 2 years.

Monkeys convalescing from a paralytic attack of poliomyelitis, according to C. W. Jungeblut (J. Infect. Dis. 58:150 (Mar.-Apr.) 1936), are uniformly insusceptible to intracerebral reinoculation with the same strain of the virus, in spite of the fact that the occurrence of virucidal antibodies in the serum during convalescence may be very irregular.

N. P. Hudson, E. H. Lennette and F. B. Gordon (J. A. M. A. 106:2037 (June 13) 1936) found neutralizing antibodies in monkeys vaccinated with certain preparations, but it is pointed out that their presence was not an indication of effective protection to intranasal virus.

According to Cohen (*loc. cit.*), monkeys which have passed through a febrile abortive cycle without paralysis, following intracerebral injection of the poliomyelitis virus in combination with an inactivating agent, are fully susceptible to intracerebral reintroduction of the virus.

S. Flexner (J. Exper. Med. 62:787 (Dec.) 1935) has found that irrespective of whether detectable symptoms of clinical poliomyelitis do or do not occur in the nasally instilled *macacus rhesus* and *macacus cynomolgus* monkeys, cerebrospinal changes quickly occur. The more common type of change is an in-

crease in cells, particularly of the lymphocytes; the less constant change is an increase in globulin. However, in spite of these changes in the cerebrospinal fluid, immunity does not develop unless clinical symptoms of infection occur. Otherwise, the animals fail to develop blood antiviral properties and they are susceptible to cerebral injection of the virus. Animals which develop immunity still continue to react to intranasal instillation of virus by changes in the cerebrospinal fluid.

According to the conclusions of Cohen (*loc. cit.*), the formation of circulatory antibodies is a by-product of poliomyelitis. Consequently, the presence or absence of virucidal substances in the serum shows little if any correlation with the resistance of the central nervous system to the reintroduction of the virus. Acquired immunity, as seen in the recovered animal, appears to depend essentially upon the presence of a local immunity factor in the nervous system itself, which, in all probability, is predominately cellular in nature. J. A. Kolmer and A. M. Rule (*J. Immunol.* 29: 175 (Sept.) 1935) state also that it is likely that resistance to poliomyelitis may be present without demonstrable amounts of antibody in the blood.

In an attempt to study this problem, F. M. Burnet (*J. Path. and Bact.* 42: 213 (Jan.) 1936) used the virus of *louping-ill*, because of the ease with which it could be detected, titrated, and studied in small animals. After intranasal inoculation in the rat, the *louping-ill* virus readily passed to the olfactory bulbs, although the rats showed no manifest evidence of infection. The virus disappeared from the olfactory bulbs after the eighth or ninth day, concomitantly with the appearance of virus—inactivating antibodies in the serum. As a rule, no further spread of virus into the central nervous system occurred

beyond the olfactory bulbs. In rare instances, trace of the virus could be found in other parts of the brain. On the basis of this study, the author suggests the hypothesis that many children exposed to poliomyelitis develop their immunity from a local infection limited largely to the olfactory bulb.

**Prognosis.**—**DEATH RATE.**—H. Meuli (*Schweiz. med. Wchnschr.* 66: 565 (June 13) 1936) states that the mortality of poliomyelitis varies between 7 and 77 per cent. In Switzerland between 1914 and 1932, the rate averaged 21 per cent. Although the morbidity in adults is less than in children, the mortality rate is higher. A. S. MacNalty (*Brit. M. J.* 2: 57 (July 11) 1936) points out that the case fatality rate varies in different epidemics; an average variation is from 10 to 20 per cent. In a group of patients studied by Barnett and Lyon (*loc. cit.*), the case fatality rate was 2.5 per cent. Leavell (*loc. cit.*) observed that the rate in an urban district was 1.7 per cent., while that in the rural community was 6.7 per cent. The death rate is also influenced by the incidence of the prevailing type of disease. C. D. Brink reports a death rate of 47 per cent. in a group of 17 patients. In all the fatal cases there was an *ascending type* of infection. All of a group of 12 patients with *bulbar lesions* and injury of the respiratory center observed by Brahdy and Lenarsky (*loc. cit.*) had a fatal termination.

**PARALYSIS.**—The incidence of paralysis is also influenced by the epidemic. Barnett and Lyon (*loc. cit.*) observed that 46 per cent. of their cases were of the abortive or nonparalytic type. On the other hand, Leavell (*loc. cit.*) observed that 70 per cent. of their urban patients and 83.3 per cent. of those from the rural district were paralyzed. E. Kramar and I. Liszka (*Monatschr. f.*

Kinderh. 60:136, 1934) report a case fatality rate of 63.6 per cent.

In the group of patients studied by Barnett and Lyon (*loc. cit.*), the cases of residual paralysis were few and the extent of the paralysis slight, with the exception of one patient. Among their patients of the paralyzed group, Meals, Hauser and Bower (*loc. cit.*) have found that to date only 20 per cent. show any residual paralysis or paresis.

E. H. Barbour (New England J. Med. 213:563 (Sept. 19) 1935) made a follow-up study of a group of 60 children, 4 years after an attack of poliomyelitis. The degree of paralysis had been previously classified under the following headings:

(a) Educationally paralyzed, implying that the individual was paralyzed to such a degree as definitely to impede his educational progress.

(b) Occupationally crippled, meaning that although the child could lead a quite normal childhood, there would be a great possibility of his paralysis prohibiting him from certain occupations in later life.

(c) *Socially handicapped*, implying a disfiguring paralysis which, although it did not interfere with his physical life, might be a source of social embarrassment to him.

In 1930, more than one-half were in the social paralysis group; approximately one-fourth in the most severely crippled, educational group; and a little less than one-fifth were described as occupationally handicapped.

In the 1934 redistribution, the paralysis in one-half of the total group had disappeared and one-half of those still crippled had only a moderate degree of paralysis. Slightly more than 1 child in 5 were occupationally crippled and only 1 in 50 was severely limited in motion.

The occupationally handicapped showed the least change. The marked decrease of the social group would seem to indicate that the child in the social paralysis group has an excellent chance of being completely normal at the end of 4 years of treatment.

Scholastically, 25 out of 40 children were not retarded in school at the end of 4 years; 9 were 1 year behind; 4 were retarded 2 years, and 1 child, 3 years.

Twenty-one children, who have completely recovered, seem to have no darker memory of the disease than if it had been measles. Among 20 children who are still paralyzed, 6 are maladjusted to the handicap.

**Treatment.**—(A) PROPHYLACTIC TREATMENT.—According to Meals, Hauser and Bower (*loc. cit.*), the problem of prophylaxis has always seemed most important but has never been satisfactorily settled. The avoiding of crowds obviously reduces the number of potential contacts. Avoiding of fatigue is also of great importance. The voluntary history of illness following swimming, particularly in hypertonic ocean water, was found to be most striking. This was thought to be due to the increase in the number of contacts and the removal of protective mucus from the nose and throat, as well as to vascular changes in the nasopharynx incident to chilling.

PASSIVE IMMUNIZATION.—According to E. B. Shaw (Northwest. Med. 35:39 (Feb.) 1936), the suggestion that convalescent serum should be injected prophylactically against poliomyelitis is to be expected. However, since the case incidence of the disease is only 1 in 1000, it would require a very large number of control and immunized cases during an epidemic in order to obtain critical evidence concerning the value of the procedure.

Meals, Hauser and Bower (*loc. cit.*) injected a group of 207 persons, consist-

ing of doctors, nurses, and hospital employees with 30 c.c. or more of **convalescent serum**. Of this number, 48, or 23 per cent., developed poliomyelitis within 3 weeks after the injections. This is an incidence far greater than that of the population at large. Fatigue and intimate contact were thought to be predisposing factors. However, the patients were on the average more seriously ill and had a more prolonged illness than those who did not receive the injections. Barnett and Lyon (*loc. cit.*), on the other hand, did not give serum to 61 children actively exposed to poliomyelitis in their homes; none developed the disease.

J. Stokes, Jr., I. J. Wolman, H. C. Carpenter and J. Margolis (Am. J. Dis. Child. 50:581 (Sept.) 1935) gave prophylactic injections of **pooled convalescent poliomyelitis serum, pooled adult serum, or citrated whole blood** to 2179 children in Philadelphia during the epidemic of 1932. The maximum quantity of whole blood for intramuscular injection was considered to be 60 c.c. A small group of 11 children contracted poliomyelitis from 5 to 8 days following the injections of blood or serum. The mild nature of the attack and the fact that residual paralysis developed only in 1 child was attributed to the use of the blood or serum. In view of their results, the authors recommend that this form of prophylactic treatment should be continued.

E. W. Schultz and L. P. Gebhardt (California and West. Med. 43:111 (Aug.) 1935; J. Pediat. 7:332 (Sept.) 1935) carried out a study to determine the protective value of immunizing **serum**. In all the experiments the serum was administered at least 24 hours preceding the inoculation of the animals. An immune horse serum of high virucidal titer was used in the majority of instances. Pooled monkey convalescent

serum and pooled normal adult human serum were also included for comparison. The majority of animals received a total of about 5 c.c. per kilo, or an amount equivalent to about 350 c.c. for the average human adult. The virus was introduced intracerebrally in one-half of the animals and intranasally in the remaining group.

M. Brodie (J. Immunol. 28:385 (May) 1935) studied the effect of **convalescent serum** in monkeys during the pre-paralytic stage of the disease. The author observed that 6 c.c. of serum given 3 days after an extracerebral infective dose prevented paralysis; 75 c.c. given within the same period after intracerebral inoculation failed to protect the animals. Their observations suggest either that the serum failed to reach the central nervous system, or that the virus was fixed in the cells and could not be dislodged.

The net protection of serum-treated animals inoculated by the intracerebral route was 23 per cent.; by the intranasal route was 92 per cent. Seventy-five per cent. of the animals, injected with immune horse serum sufficient to neutralize at least 200,000 m. i. b. of virus, failed to resist 100 m. i. d.'s or more of the virus; while 25 per cent. failed to resist 10 m. i. d.'s of virus. It is, therefore, apparent that for protection against a given dose of virus a proportionately higher concentration of antibodies is necessary.

The convalescent serum proved less effective than the immune horse serum; the pooled adult serum was least effective.

While the immunizing serum seemed to have an effect of prolonging the incubation period, once the infection was established, the serum did not appreciably alter the course of the illness. Serum administered 2 or more days after inoculation with the virus was without



power to modify the course of the infection.

**ACTIVE IMMUNIZATION.—Vaccines.**—According to T. M. Rivers (Am. J. Pub. Health 26:136 (Feb.) 1936), the virus of poliomyelitis, either active or inactive, acts as though it were a poor antigen. Even large amounts of it in the active state, administered intracutaneously or subcutaneously, do not regularly produce resistance to infection in monkeys.

(A) *Brodie-Park Vaccine*.—M. Brodie and W. H. Park (*Ibid.* 26:119 (Feb.) 1936; J. A. M. A. 105:1089 (Oct. 5) 1935) have found that a formolized vaccine produces some antibody response in both monkeys and human beings. The vaccine is apparently safe, because it fails to infect monkeys after intracerebral inoculation. The combined humoral and tissue immunity of children, according to the authors, can be tested only in following up the outcome of natural exposure.

Up to the present time, while 5 of a smaller control group became infected with poliomyelitis, apparently only 1 of a group of 7000 vaccinated children has contracted the disease; this patient developed poliomyelitis 14 days after the first injection. Reynolds and Knox (*loc. cit.*) state that so far nothing has been learned from the vaccination of 300 children in the city of Greensboro, North Carolina. No case in the vaccinated or the control group has contracted the disease; assuming that the vaccine is 100 per cent. effective, the authors question whether the procedure is a wise public health measure.

P. K. Olitsky and H. R. Cox (J. Exper. Med. 63:109 (Jan.) 1936) state that it is a question whether any form of inactive virus retains the property of immunizing animals. The amount of antiviral substance in monkeys following the injection of formolized vaccine was so slight that the animals failed to show

immunity by the intranasal or intracerebral test.

(B) *Kolmer Vaccine*.—J. A. Kolmer (Am. J. Pub. Health 26:126 (Feb.) 1936; J. A. M. A. 105:1956 (Dec 14) 1935) employed a 4 per cent. remote monkey passage virus treated with 1 per cent. sterile solution of sodium ricinoleate and more recently with 1:80,000 phenyl-mercury nitrate. That immunity rapidly develops following injections of the vaccine seems to be shown by the fact that monkeys vaccinated by this method are effectively protected against experimental poliomyelitis when injected during the incubation period.

P. K. Olitsky and H. R. Cox (*loc. cit.*), used tannin precipitated virus and virus treated with sodium ricinoleate in an attempt to vaccinate *macacus rhesus* monkeys against poliomyelitis. It was found that a sufficient amount of virus was present to give rise to the danger of infecting the animals. Furthermore, while serum antiviral bodies were produced by this method, they apparently were not sufficient to prevent infection by the ordinary tests.

J. F. Kessel (Am. J. Pub. Health 26:145 (Feb. 1936) vaccinated 70 members of a group of 144 nurses either with the Brodie or the Kolmer vaccine. Three or four days after the first injection 1 patient treated with the Brodie, and another treated with the Kolmer vaccine, as well as a control patient, developed poliomyelitis.

The authors contended that all these patients were in the incubation period of poliomyelitis when the vaccine was injected. In a second group of 42 vaccine treated nurses, no case of poliomyelitis developed, while 3 cases occurred among 50 persons constituting the control series.

According to Kolmer (*loc. cit.*), the vaccine has been employed in the immunization of 10,725 individuals. No

person who received the 3 full doses developed the disease. However, 10 cases of poliomyelitis followed the first or second injection. An analysis of these cases indicated, according to the author, that some of the patients were in the incubation period of poliomyelitis when the administration of the vaccine produced a *negative phase*, thus lowering the patients' resistance to infection. The author feels that the vaccine is probably safe for the immunization against poliomyelitis. However, H. F. Vaughan (Am. J. Pub. Health 26:143 (Feb.) 1936) and J. P. Leake (*Ibid* 26:148 (Feb.) 1936) contend that the 10 cases of poliomyelitis which followed attempts of immunization were probably produced by the vaccine virus. Leake urges that the *use of the vaccine in human beings be discontinued*. He has reported (J. A. M. A. 105:2152 (Dec. 28) 1935) 12 cases of poliomyelitis which have followed one or the other type of poliomyelitis vaccine.

CHEMICAL AGENTS.—E. W. Schultz and L. P. Gebhardt (Proc. Soc. Exp. Biol. and Med. 34:133 (Mar.) 1936) irrigated the nasal passages of monkeys with 1 per cent. **picric acid** on 3 successive days. Without further treatment, 10 animals exhibited a well-defined resistance to intranasal instillation of the virus for a period of from 2 to 69 days; 1 developed the disease with the first instillation. In the control group, 90 per cent. of the animals contracted poliomyelitis. For fairly uniform results, repeated washings with picric acid are necessary.

A 1 per cent. solution of **p-nitrophenol** and a similar strength solution of **trinitrocresol** used intranasally seemed to be effective for at least 2 days; a 1 per cent. solution of **ammonium picrate** apparently had no protective value.

**Sodium alum** or **tannic acid**, in proper concentration, when instilled in-

tranasally for at least 3 days, will induce effective resistance to nasal inoculation with the virus. A. B. Sabin, P. K. Olitsky and H. R. Cox (J. Exper. Med. 63:877 (June) 1936) point out that once the resistance is developed, it does not disappear quickly when the instillation of the chemical is repeated daily. Four per cent. tannic acid or sodium alum can be given to human beings with only slight discomfort and no apparent harmful effect.

C. Armstrong and W. T. Harrison (Pub. Health Rep. 51:203 (Feb. 28) 1936) determined the relative value of various chemical agents in protecting white mice against the intranasal introduction of the encephalitis virus. The solution found most effective in this experiment was then studied to determine its protective value against experimental poliomyelitis.

The following agents were compared: *Cobra venom, sodium chloride, distilled water, alum, formalin, glucose, zinc chloride, aluminum chloride, picric acid, tannic acid, lead acetate, sea water, picramic acid, dinitrocresol, dinitrophenol, and quinine hydrochloride* were used in one or more concentrations, and either alone or combined with other substances. Picric acid, 0.32 to 0.64 per cent., either alone or combined with alum, was found superior to 4 per cent. alum and was the most satisfactory and efficient agent tried. Sixteen applications sprayed by means of an atomizer into the nostrils of the author produced no deleterious or injurious effect. Consequently, **picric acid** was utilized in an attempt to prevent intranasal inoculation of poliomyelitis in monkeys.

When given 1 to 2 days before, 1 to 2 days after, or on the same day of the virus instillation, picric acid led to a decreased susceptibility to the virus in all instances as compared with nonprepared controls. The protective action of

the acid seems to persist for at least 4 to 7 days following its last administration. It is believed either that the chemical affects the mucous membranes, rendering them less permeable to infection, or that it possibly acts upon the virus itself.

In contrast with the observations of Sabin, Olitsky and Cox (*loc. cit.*), using tannic acid or sodium alum, in preventing poliomyelitis in monkeys, Armstrong and Harrison observed that picric acid does not prevent the development of specific immunity in mice following subsequent intranasal instillation of encephalitic virus.

**NASAL SPRAY IN HUMAN BEINGS.**—According to reports from the U. S. Public Health Service (J. A. M. A. 107:363 (Aug. 1) 1936), the evidence in regard to the use of a nasal spray as a preventive of poliomyelitis is based entirely on animal experimentation. The proposed spray is not at present to be regarded as of proved value in the prevention of poliomyelitis in man. It may be advisable to await the results of further trials before giving the method general application.

If it is desired to use the solution, it should be sprayed into the nostrils 3 or 4 times on alternate days, and thereafter weekly, during the presence of poliomyelitis. The spray tip should be pointed upward and backward at an angle of about 45 degrees, and the spraying should be thorough enough to reach the pharynx, when a bitter taste will be noted. The early application at least should be administered by a physician. The tentative procedure is subject to such changes as may be indicated by future findings.

The most effective solution so far developed during the experimentation on monkeys, is prepared as follows:

**Solution A.**—Dissolve 1 Gm. (15 grains) of **picric acid** in 100 c.c. (3½ ounces) of physiologic salt solution

(0.85 per cent.). (Warning facilitates solution of the picric acid.)

**Solution B.**—Dissolve 1 Gm. (15 grains) of **sodium aluminum sulphate** (sodium alum) in 100 c.c. (3½ ounces) of physiologic salt solution (0.85 per cent.). Any turbidity in this solution should be removed by filtering one or more times through the same filter paper.

Mix solutions A and B in equal amounts. The resulting mixture, which contains 0.5 per cent. picric acid and 0.5 per cent. alum, is sufficiently antiseptic to prevent the growth of organisms and is ready for use as a spray. Homemade concoctions are not favored.

**Complications.**—L. J. Rutledge (J. A. M. A. 107:1322 (Oct. 17) 1936) observed 2 cases of nephritis in human beings which apparently were due either directly or indirectly to the use of the picric acid-alum spray.

**IMMUNITY TESTS.**—**Skin Test.**—The intracutaneous injection of attenuated monkey passage virus, according to J. A. Kolmer, G. Klugh, Jr. and A. M. Rule (J. Immunol. 29:191 (Sept.) 1935) cannot be employed as a test for immunity to poliomyelitis.

**Serum colloidal gold, complement fixation and precipitation tests** cannot be employed to determine susceptibility or immunity to poliomyelitis.

**Neutralization Tests.**—The only antibody known at present to bear a definite relationship to resistance and immunity is that occurring in serum capable of neutralizing virus *in vitro*, and designated as *antiviral antibody*. The presence of an amount of antibody in 0.5 c.c. of serum neutralizing at least 10 minimal injective doses of monkey passage virus is believed to indicate effective resistance to poliomyelitis. However, C. W. Jungblut (J. Exper. Med. 62:517 (Oct.) 1935) has pointed out that in view of the fact that poliomyelitis virus is rendered noninfectious by small doses

of vitamin C, investigations will have to show whether the neutralization phenomenon observed with certain serums may be influenced by vitamin C in the serum.

(B) THERAPEUTIC TREATMENT.—(a) *Convalescent and Pooled Adult Serum; Rosenow's Serum*.—Schultz and Gebhardt (*loc. cit.*) have observed that serum administered 2 or more days after the inoculation of animals with poliomyelitis virus is without power to modify the course of the infection. However, P. H. Harmon and H. N. Harkins (J. A. M. A. 107:552 (Aug. 22) 1936) state that convalescent and other specific serum therapy should be used, as there is no evidence that they are not of value. The authors state that the symptomatic improvement following their use is almost universal. Meals, Hauser and Bower (*loc. cit.*) agree that little is to be expected from the use of convalescent serum after the central nervous system has been invaded beyond the stage of inflammation. However, the authors feel that the serum is of value if used in the preparalytic stage; the rapid abatement of symptoms following its use are quite striking.

Barnett and Lyon (*loc. cit.*) treated 29 patients with convalescent serum in the preparalytic stage of the disease. Of this group, only 9 children became paralyzed; only 1 of these has a residual severe, and permanent paralysis. Of 14 children seen or diagnosed after paralysis, 3 still have a residual paralysis; in 1 child the residual paralysis is almost complete. It is pointed out that there is no way of determining how many, if any, of the 20 children who escaped paralysis would have escaped without the use of serum.

In all cases in which the disease was recognized in the acute stage, J. C. Wilson and P. J. Walker (Arch. Int. Med. 57:477 (Mar.) 1936) gave serum. Of 14 patients with some degree of

residual paralysis, all but 1 received serum. However, according to the authors, there was a definitely higher incidence of motor recovery in the serum-treated group. The authors alternated convalescent serum with pooled adult serum. B. F. Howitt (California and West. Med. 43:407 (Dec.) 1935) has concluded that in the advent of a sudden epidemic, it would seem justifiable to use pooled adult serum obtained from an urban district.

W. W. Nicholson (Kentucky M. J. 34:115 (Mar.) 1936) observed a group of 108 cases of poliomyelitis. Sixty-two, or 56.6 per cent. were admitted without paralysis. Of the 62 patients, 43, or 70 per cent., remained free of paralysis. Thirty-one of the patients received no special form of treatment; 24, or 77 per cent., remained normal. Nineteen were given forced perivascular drainage, first described by G. M. Retan (J. A. M. A. 105:1333 (Oct. 26) 1935); 13, or 68 per cent., did not become paralyzed. Twelve were given Rosenow's serum; 7, or 58 per cent., were of the nonparalytic type of the disease.

*Petit Serum*.—The injection of horses with virus containing spinal cord will give rise to an antiviral serum in approximately 30 per cent. of the animals. When used in the preparalytic stage of poliomyelitis, it is said to be of definite therapeutic value in the prevention of paralysis (Italian Correspondent: J. A. M. A. 105:1700 (Nov. 23) 1935).

R. Southby (M. J. Australia 2:367 (Sept. 21) 1935) states that the only conclusion that can be drawn in regard to serum therapy is that it may be of some benefit and it has no harmful effect. Therefore, he advises that its use be continued until more convincing evidence is available. J. MacNamara (*Ibid.* 2:374 (Sept. 21) 1935), in the absence of a better therapeutic agent, also recommends the use of convalescent serum.

*Route of Injection.*—Barnett and Lyon (*loc. cit.*) administered 20 c.c. of pooled convalescent serum intravenously. Wilson and Walker (*loc. cit.*) administered the serum intramuscularly or intravenously. In addition to the intramuscular and intravenous routes. Meals, Hauser and Bower (*loc. cit.*) also administered the serum intrathecally. Southby (*loc. cit.*) administered the serum either intravenously or intramuscularly. An initial dose of 25 to 30 c.c. of convalescent serum is advocated for children up to 5 years of age; 45 to 60 c.c. for children from 6 to 15 years; and 90 to 120 c.c. for older children. The dose may be repeated in 24 hours. Following an initial intravenous dose of 50 to 100 c.c., Shaw (*loc. cit.*) recommends that the dose should be repeated at 12- to 24-hour intervals during the preparalytic stage.

*Immune-transfusion.*—Shaw (*loc. cit.*), in addition to the use of serum, also recommends transfusion of convalescent or normal blood. Meals, Hauser and Bower treated 60 patients by means of blood transfusions from immune donors. In this group, 8 per cent. reacted badly to the treatment. The group as a whole was more acutely ill and remained longer in the hospital than a control group of more severely toxic patients treated intravenously with 10 per cent. dextrose in physiological saline. The authors conclude that immune-transfusion should be used only when the central nervous system is involved and should not be carried out during the early systemic phase.

*Rabies Vaccine.*—E. Barla-Szabó (Wien. klin. Wchnschr. 48:81 (Jan. 18) 1935) has used rabies vaccine in the treatment of 17 cases of poliomyelitis in the paralytic stage of the illness. The vaccine was used because of its affinity for nervous tissue and because he believes it has an action antagonistic to the

poliomyelitis virus. His dragging but inconclusive results were obtained by the author.

*ORTHOPEDIC TREATMENT.*—For convenience, the orthopedic treatment of poliomyelitis may be divided into 3 stages: (1) the acute stage; (2) the convalescent stage; (3) the stage of residual paralysis.

1. *Early or Acute Stage.*—During the preparalytic stage, muscle tenderness is often elicited by pressure, or by active or passive motion. Treatment at this time, according to A. M. Rechtman (Arch. Phys. Therapy 16:411 (July) 1935), should be directed toward **keeping the parts warm** and maintaining them in a **neutral muscle position**. A. Faber (Munchen. med. Wchnschr. 82:91 (Jan. 17) 1935) states that a paralyzed muscle regains its function only when the contracture of the antagonistic muscle is prevented. With the onset of the paralysis, **rest** and the **prevention of deformity** are essential until all soreness and tenderness have disappeared, which usually require about 6 weeks (Rechtman: *loc. cit.*) or 2 months (R. T. Hudson; Kentucky M. J. 34:117 (Mar.) 1936).

As soon as weakness or paralysis occurs, A. T. Legg (New England J. Med. 213:415 (Aug. 29) 1935) has outlined the following recommendations:

#### 4. To Prevent Deformity:

1. **Posterior wire splint for the legs** to hold them in their normal position.
2. A **corset** to hold the trunk in normal position.
3. A **platform splint to hold the arm in abduction** to prevent any strain on the weakened deltoid.
  - (a) 1. The **elbow** may be **flexed or extended**, depending upon the power in the biceps or triceps.
  - (b) 2. A **hand splint** to prevent deformity of the hand.

*B. To Relieve Sensitiveness:*

1. **Hot packs**, 2 or 3 times a day.
2. **Complete rest.**

No massage or manipulation should be allowed during the sensitive stage.

*Second or Convalescent Stage.*—According to Hudson (*loc. cit.*), this period begins with the disappearance of muscle soreness and ends when further muscular improvement ceases to occur. This stage is usually considered to be 2 years in duration. During this period Rechtman (*loc. cit.*) states that the judicious use of **physical therapy** is valuable, and **braces** and **splints** aid in protecting the weakened structures against deformities.

According to Legg (*loc. cit.*), a complete muscle examination should be made as soon as the sensitiveness is over. **Muscle training** should then be started to strengthen the weakened muscles by carrying out their function voluntarily. This procedure should be increased gradually. Over-fatigue should be guarded against. Treatment in water is not a specific form of therapy, although it is a pleasant way of doing exercises. Muscle training, preceded by **baking** and **massage**, should be carried out only by a worker with a thorough knowledge of functional anatomy. Frequent muscle examination should be made in the beginning, to determine gain or loss in power; the treatment should then be adjusted accordingly.

**Electrical stimulation** with a response in the involved muscle is not as effective as a voluntary contraction. A muscle that responds to electrical stimulation can usually produce voluntary motion. The dangers from this type of stimulation are not only from over-fatigue of the muscle without reëducation of the nerve pathways, but also from the fact that stimulation strong enough to produce a response from muscles too weak to respond well vol-

untarily, is likely to spread to other and stronger muscles.

Patients should never be permitted to stand in a deformed posture; **splints** should be applied to keep knees and feet in their normal position; a **corset** or **jacket** should be used to retain the normal position of an involved spine. Patients should not be encouraged to walk soon after the onset or to use mechanical exercises. All patients should be followed for years to determine any unbalance of muscle power.

*Third Stage, or Period of Residual Paralysis.*—This period persists during the remainder of the patient's life.

Hudson (*loc. cit.*) has outlined the following commonly used operations for improving function:

1. **Arthrodesis.**
2. **Stabilizing operations.**
3. **Transplantation of tendons; tendon lengthening.**
4. **Osteotomies** to correct deformities.
5. **Bone lengthening and bone shortening operations.**

The real place of operative interference, according to Rechtman (*loc. cit.*), is after the maximum amount of spontaneous recovery has occurred. **Arthrodesis**, or the fusion of two or more bones, permits of greater stability where normal muscle balance has been disturbed by paralysis. Such operations are best done after the age of 12 years. **Tendon transplant** may serve as a temporary measure before this age. **Stabilizing operations** upon the bones have proved more efficient and enduring than surgery upon soft structures. Nerve operations have practically been abandoned as of no value. According to the author, *muscle* and *tendon* transplant, especially with arthrodesis, are most frequently practiced in the foot. Transplantations at the shoulders and

elbow joints have usually proved disappointing.

An **astragalectomy** with backward displacement of the foot is a satisfactory method of stabilizing the ankle. A **Campbell's bone block**, or the operation as modified by **Gill** (T. F. Wheelton and M. M. Clark (J. A. M. A. 106: 447 (Feb. 8) 1936), is an adequate means of correction of *foot drop*. **Rechtman** states that a **subastragalar arthrodesis** is perhaps the best means of stabilizing a foot with lateral deformity, as varus or valgus. **Arthrodesing** operations of the ankle joint are seldom done because a stiff ankle is uncomfortable and ungainly. Fusion of the posterior arches and spinous processes of the spine prevents the increase of a scoliotic deformity. Fusion of the shoulder joint is sometimes indicated. Arthrodesis at the knees, hip and elbows is seldom indicated.

*Flexion deformity of the hip* and its treatment has been discussed by G. deN. Hough, Jr. (Surg. Gynec. and Obst. 61: 90 (July) 1935). The author has used 5 methods of correction, combined to form 8 groups, *viz.*, (1) **stretching**; (2) **subcutaneous tenotomy** at the hip; (3) **subcutaneous tenotomy** of the iliotibial band; (4) this procedure combined with **fasciotomy** at the hip; (5) often **division of the iliotibial band**; (6) this combined with **subcutaneous tenotomy** at the hip; (7) the same combined with **fasciotomy** at the hip; and (8) **fasciotomy** at the hip alone. Over 95 per cent. of the cases encountered by the author were included in the last four groups.

*Leg Lengthening*.—G. B. Stephenson and H. A. Durham (South. M. J. 28: 818 (Sept.) 1935) carefully selected 17 patients with at least fair muscle control of the thigh and leg. In 15 of these patients, the tibia and fibula were lengthened; in 2, the femur. The au-

thors conclude that the lengthening of the tibia and femur are procedures of great value in carefully selected cases.

*Lumbar Sympathectomy*.—R. I. Harris and J. L. McDonald (J. Bone and Joint Surg. 18:35 (Jan.) 1936), as well as A. W. Adson (J. A. M. A. 106: 360 (Feb. 1) 1936), have found lumbar sympathectomy of value in the treatment of a paralyzed lower extremity. The operation leads to an increase in blood supply to the involved part and a resulting acceleration in growth.

In order to obtain satisfactory results, Harris and McDonald (*loc. cit.*) recommend that:

(a) The paralysis be limited to one lower extremity.

(b) The paralysis be moderate in degree.

(c) The operation should be performed early in life—at the age of 6 years, if possible.

(d) A ganglionectomy rather than a ramisection be performed.

(e) A maintenance of the increased vascularity which follows the operation.

**RESPIRATORY DIFFICULTY**.—M. B. Brahdy and M. Lenarsky (J. Pediat. 8: 420 (Apr.) 1936) point out that respiratory difficulty in poliomyelitis may be caused by (1) paralysis of the respiratory center; (2) paralysis of the diaphragm or intercostals, either separately or in combination, or (3) accumulation of saliva and mucus in the pharynx in patients who are unable to swallow.

According to Brahdy and Lenarsky (*loc. cit.*) and to R. T. Hudson (Kentucky M. J. 34:117 (Mar.) 1936), patients with paralysis of the respiratory center, as well as those whose respiratory difficulty is due to pharyngeal paralysis, are not benefited by the use of the *respirator*. In fact, the *respirator* may prove injurious under these conditions. Shaw (*loc. cit.*) states that patients with involvement of the respira-

tory center are seldom able to adjust themselves to the rhythm of the machine. The respirator is useful only in patients with paralysis of respiratory muscles involving the diaphragm and thoracic muscles, due to lesions in the spinal cord.

Patients of the third group, because of the difficulty in swallowing, should be placed **face downward with the head low and feet elevated** in order to enable the saliva to flow from the mouth. During the earlier stage, **fluids** should be given **by rectum or subcutaneously**. However, if difficult swallowing persists feedings then may be given **by gavage**. When gavage is used, the

danger of regurgitation and aspiration must be kept in mind.

Patients of this second group who have only slight evidence of respiratory difficulty, without dyspnea or cyanosis, should not be placed in a respirator. The author's opinion is based on the present knowledge of the physiology of respiration, the pathologic pulmonary conditions found in patients after treatment in the respirator, and the late pulmonary complications occurring in patients who survive the treatment. Patients of this type, however, should be in a hospital near a respirator in case one is needed.

## DISEASES OF THE RESPIRATORY SYSTEM IN CHILDREN

By WALDO E. NELSON, A.B., M.D.

**UPPER RESPIRATORY INFECTIONS.—Treatment.**—The following recommendations for the management of the "cold problem" in infants and small children are made by Y. Kneeland, Jr. (M. Clin. North America 19:745 (Nov.) 1935):

1. The **isolation** of the affected child or adult in the homes, and the removal of all infected children from school or kindergarten.

2. Local measures: (a) There is no theoretical or practical evidence that "sterilization" of the mucous membranes during an acute cold is possible. (b) Nasal constrictor drugs which shrink the mucous membranes and therefore promote drainage of the paranasal sinuses, are helpful if not used in too strong solutions or over too long a period of time. The use of 0.5 per cent. of **ephedrine** is suggested. (c) General **suction with a soft rubber bulb** may be helpful in removing nasal secretions from infants. (d) Bland nonirritating nose drops, such as simple **alboline**, may be beneficial where there is much excoria-

tion of the nares, although oily substances may block the normal drainage of secretions. The danger of pulmonary irritation from oil must be borne in mind.

3. While there is no evidence to prove that well nourished children have greater resistance to upper respiratory infection than do the undernourished, **good nutrition** should be **encouraged**.

4. There is no evidence to show that amounts of **vitamin A** in excess of the ordinary infant diet or of **vitamin D** over that given as an antirachitic, have any prophylactic value against respiratory infections.

5. Indoor **clothing** should be light and additional warmth for out of doors should be supplied by outer clothing.

6. Since there is no method, at present, for immunization against the virus of the common cold, the question is raised whether there is any value in attempting to immunize against secondary invaders. The author suggests the use of **vaccine** made from the pneumococci (Type VI, XIV and III), H. influenzae and hemolytic streptococci. The



vaccine should contain approximately 1 billion organisms per c.c. The course of injections should be commenced early in the autumn, starting with 0.1 c.c. and working up by tenths to the maximum of 1 c.c. It is advised to give the injections twice weekly for 2 or 3 weeks, and then at weekly intervals for a longer period of time, perhaps, for the entire winter. This latter procedure is advised only for the small group of children who are highly susceptible to respiratory disease.

**LARYNGEAL STRIDOR.**—An instance of congenital hyperplastic redundancy of the normal subglottic mucous membrane of the infantile larynx sufficient to cause obstructive dyspnea is reported by J. Glaser, D. B. Landau and C. A. Heatly (Am. J. Dis. Child. 50:1203 (Nov.) 1935). As far as the authors could determine, this is the first reported case of this type. The outstanding symptom was recurrent attacks of marked *dyspnea*. Unfortunately, the presence of a large thymus gland drew attention from the larynx to the thorax. After several x-ray treatments and finally thymectomy, a tracheotomy was performed with immediate relief of the dyspnea. Subsequently, direct laryngoscopic examination revealed within the subglottic space a thick band of somewhat reddened tissue projecting beneath each vocal cord and reducing the lumen to a narrow opening. The subsequent treatment consisted of periodic **dilation of the subglottic obstruction**, starting with a No. 14 metal bougie and gradually increasing to a No. 24. Nine treatments were given over a period of 16 weeks. The child was prepared for the procedure by small doses of **phenobarbital** and **atropine**. After 13 weeks of treatment, the tracheotomy tube was removed. The infant was examined at the age of 9 months, apparently about 2 months after the hospital

dismissal. At this time breathing was normal and the subglottic bands appeared to have retracted to the edges of the vocal cords.

**PNEUMONIA.—Epidemiology.**—J. J. Bunim and J. D. Trask (Am. J. Dis. Child. 50:626 (Sept.) 1935) have carried out an epidemiologic study in families of children with pneumococcal lobar pneumonia. Their observations do not differ materially from those of other investigators who have found that there is an increased carrier rate of the pneumococcus among members of families in which there is a case of pneumococcal pneumonia. In the authors' experience there was an increase in the incidence of carriers of heterologous as well as homologous types of pneumococci. There was a distinct relation between the presence of symptoms of infections of the upper respiratory tract and the presence of the carrier state of homologous and heterologous pneumococci. Both the incidence of upper respiratory infection and the presence of the carrier state were found to be more frequent in the younger members of the family.

**Typing of Pneumococci.**—The importance of accurate classification of pneumococci is stressed by R. L. Nemir, E. T. Andrews and J. Vinograd (*Ibid.* 51:1277 (June) 1936) from the standpoint of both prognosis and treatment. Complications and mortality are said to be definitely related to the type of infecting organism. In the authors' experience, specific serum therapy is most effective against pneumonia caused by Types I, XIV, V and VII. Fortunately, these are types frequently encountered in patients with lobar pneumonia and are associated with disease of marked severity.

A method for the rapid typing of pneumococci by the *Neufeld reaction*, in which the material is taken directly from laryngeal swabs, is described by J.

Vinograd, R. L. Nemir and W. H. Park (*Ibid.* 51:792 (Apr.) 1936). The comparison of this method with other routine methods of typing was also made. By the Neufeld reaction, the type of pneumococcus can be determined for children and infants within an hour. The authors conclude that the Neufeld technic is the most rapid method of typing pneumococci and is as accurate, if not more so, than any of the other available technics.

Their technic is as follows:

Coughing is induced by irritating the pharynx with a swab or tongue depressor. One or two swabs are collected and inserted in a 2 x 10 cm. test tube containing from 1.5 to 2 c.c. of nutrient broth containing 0.2 per cent. di-sodium hydrogen phosphate. The specimen is taken immediately to the laboratory. Particles of sputum are thoroughly removed from the swab by whirling the stick rapidly back and forth in the broth a number of times.

For the Neufeld procedure, the tube of broth containing the original material is centrifuged at high speed for from 5 to 10 minutes to sediment the particles of sputum, pus cells and organisms. All but 1 or 2 drops of the supernatant fluid are decanted and retained for further use. A loopful of the sediment is mixed on a cover slip with 2 or 3 loopfuls of type-specific rabbit serum and a loopful of Loeffler's alkaline methylene blue. The preparation is then examined as a hanging drop under oil for the *Quellung* (swelling of the capsule) phenomenon.

The use of *gastric aspiration* in children with pneumonia to obtain material for *pneumococcus typing* has been suggested by S. A. Wittes and J. G. M. Bullova (*Ibid.* 50:1404 (Dec.) 1935). It has been demonstrated repeatedly that tubercle bacilli of pulmonary origin may be found in the gastric contents. Even in the absence of cough, pulmonary secretion is carried by peristalsis and ciliary action to the epiglottis, where it overflows into the esophagus. In the acid content of the stomach, the mucus is not dissolved. While the authors have been

successful in obtaining material for typing by gastric aspiration, they have not been successful with gastric lavage. Their method is as follows:

The equipment consists of a 50 c.c. rubber tube, 4 mm. in diameter, with a 2 mm. bore, a 20 c.c. Luer syringe, a Petri dish, 10 c.c. of distilled water, and typing serums for the several types of pneumococci.

The child is wrapped in a mummy bandage and the rubber tube is introduced into the stomach. Suction is then applied with the syringe. If the thick mucoid secretion does not enter the syringe, as usually happens, an alternating vacuum is created by repeated partial withdrawing of the piston of the syringe. The small rubber tube is then withdrawn from the stomach, meanwhile maintaining a vacuum in the syringe in order to retain any mucus adhering to the opening or to extract any mucus in the esophagus. The stomach end of the tube is placed in a test tube containing 10 c.c. of sterile saline solution so that the mucus in the tube may be flushed into the syringe. The contents of the syringe are then discharged into a Petri dish. Flecks of mucus are examined directly by means of the Neufeld swelling reaction.

In a series of infants and young children with pneumonia, the method of gastric aspiration was shown to be definitely more accurate in obtaining the causative organisms than was either the throat swab or the lung puncture method.

**Immunity.** — In agreement with the majority of observers, D. Greene (*Ibid.* 51:284 (Feb.) 1936) states that children may have more than one attack of pneumonia. From his observations he concludes, however, that one attack of the disease does confer some degree of increased resistance to subsequent attacks. Whether this is true or not is not apparent from his observations, since his mortality rate for subsequent attacks must be compared to the group of children who have survived an initial attack. The mortality rate in this group is, of course, zero.

**Treatment.**—A clinical study of the treatment of lobar pneumonia in children by artificial pneumothorax has been made by P. Harper (*Ibid.* 51:536 (Mar.) 1936). No claims are made for the value of this form of therapy. The report deals primarily with the develop-

a rise in the interpleural pressure averaging  $-4$  cm. of water was observed when patients who had been lying on their sides during the injections of air were turned to lie on their backs, it was deemed best to treat the children in the spine position. The needle was inserted

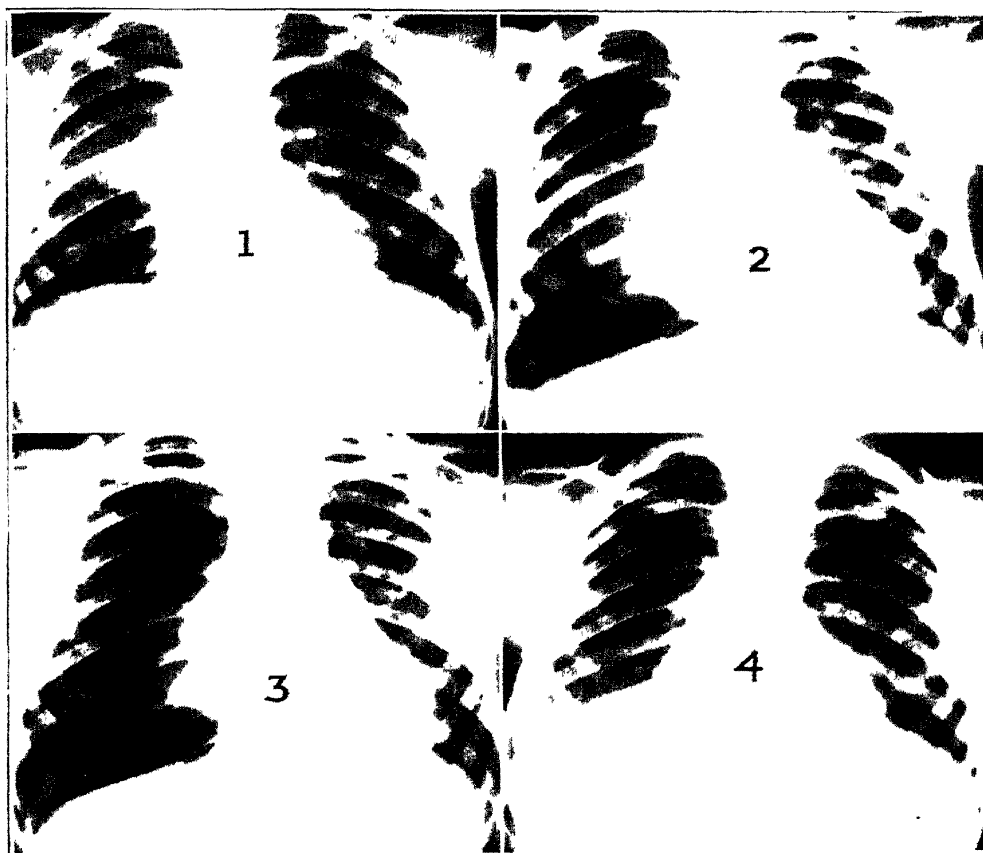


Fig. 1.—Serial roentgenograms, showing: 1, condition before treatment, with early infiltration; 2, fair collapse after 750 c.c. of air was injected during the first 10 hours of therapy (note small adhesion holding out lower lobe of right lung); 3, more collapse in spite of persisting adhesion; and 4, reexpansion nearly complete on twenty-fifth day, with a small pleural effusion. (Harper: *Am. J. Dis. Childhood.*)

ment of the technic for this procedure and with clinical and x-ray observations during the period of lung collapse. There were no fatalities in a group of 22 children, ranging in age from 15 months to 15 years, who were treated with artificial pneumothorax. The question of sedation is an important one and after trying several different sedatives the author concluded that **morphine** gave the most satisfactory results. Since

in the third or fourth interspace between the midaxillary and the anterior axillary line.

In general, it was felt that the results of compression of the pneumonic lung were encouraging when early and good collapse was obtained and were of doubtful value when compression was either delayed or incomplete. Fig. 1 is illustrative of the changes observed during the course of treatment.

More complete and rapid compression of the lung without discomfort to the patient was obtained by decreasing the rate of injection of air from 10 to 12 c.c. per minute to a speed of from 7 to 9 c.c. per minute, and by increasing the amount of air injected, especially at the initiation of pneumothorax. It is suggested that interpleural pressure needed to give early and satisfactory collapse varies both with the age of the child and with the extent of the pneumonic infiltration. From fair to good collapse was obtained in a patient under 3 years of age with a mean pressure of  $+2$  cm. of water, in 5 patients from 4 to 6 years of age with a mean pressure of from  $+4$  to  $+5$  cm. of water, and with 5 older children with a mean pressure between  $+5$  and  $+7$  cm. of water. These levels of pressure were obtained by introducing a large amount of air at a slow rate during the first 12 to 18 hours. The volume of air injected by the author on the initiation of pneumothorax in his last 4 patients, age 15 months and 6, 8 and 13 years, respectively, was 150 c.c., 650 c.c., 650 c.c. and 850 c.c., respectively. The air was injected at a rate of from 7 to 9 c.c. per minute. The average interval between the first and second injection was 4.3 hours. Rapid and satisfactory compression was obtained in all except the 15 months' old child, in whom the interpleural pressure was not raised beyond zero during the first 12 hours. During the injection of air, reliance was placed on the symptomatology, especially beginning dyspnea, and on evidence of mediastinal shift for warning to stop. In all instances respiratory distress passed away within a few hours. When re-injection of air was commenced after an interval of about 4 hours, the pressure was carried to higher levels without causing disturbing symptoms.

It is necessary to rely on the x-rays for the extent of the collapse in the course of pneumonia, since the usual physical signs are obscured and altered after institution of the pneumothorax. X-ray examination is also necessary for the diagnosis of mediastinal hernia and of adhesions, and particularly to differentiate between preëxisting fibrous pleural adhesions and temporary adhesions formed during the course of pneumothorax.

The author's experience suggests that when preëxisting and fibrous *adhesions* are present to an extent to prevent good collapse, pneumothorax should probably be discontinued. However, when temporary adhesions develop during the course of artificial pneumothorax, the maintenance of the interpleural pressure at a positive level to favor separation and to decrease the danger of permanent adhesions developing from the temporary ones is advised.

*Changes in lung volume* during treatment with **artificial pneumothorax** for lobar pneumonia were studied by G. E. Lindskog, P. Harper and I. Friedman (*Ibid.* 51: 523 (Mar.) 1936). It was observed that lobar pneumonia was associated with a reduction in subtidal volume of the lungs early in the disease, as compared with the values during convalescence. The introduction of measured quantities of air in one pleural cavity resulted in a decrease in the subtidal volume of the lungs, but always quantitatively less than the volume of introduced air. Similarly, the withdrawal of air from the pneumothorax cavity resulted in a rise in the subtidal volume, but less than the amount of air removed. There was no failure of the mechanism of external respiration even in the presence of infection in the respiratory tract, when the subtidal volume was gradually reduced to a level only 50 or 60 per cent. of the normal.

**LOBAR COLLAPSE.**—A series of cases of lobar collapse in children is reported by G. L. Boyd (J. A. M. A. 105:1832 (Dec. 7) 1935). All of these cases were associated with *bronchiectasis*, and exhibited basalar triangular shadows on the roentgenogram. These shadows are described as homogeneous, opaque

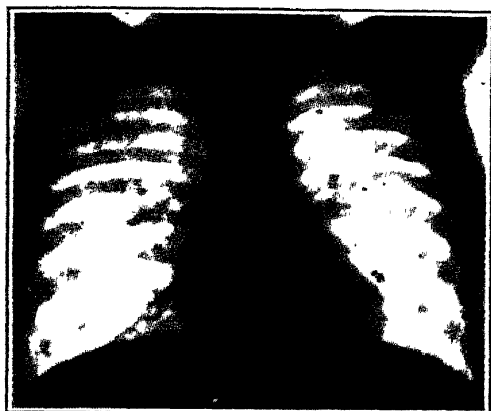


Fig. 2.—X-ray appearance April 21, 1933, at 10 years of age. (Boyd: J. A. M. A.)

shadows in the form of a right angle triangle having for its base the diaphragm, for one side the mediastinum and for the hypotenuse a line extending from the hilum to some point on the diaphragm. Such basalar triangular shadows in roentgenograms of children's chests are said to be due to lobar collapse. The author points out that such collapse is usually associated with bronchiectasis and while it is not pathognomonic of this disease, it is highly suggestive. The lobar atelectasis is the result of infection or injury of the bronchial wall, with secretion and consequent plugging of the bronchioles. Fig. 2 shows the roentgenogram of one of the author's cases demonstrating a bilateral lobar collapse.

**ALLERGIC PNEUMONIA.**—It has been suggested by H. Miller, G. Piness, B. F. Feingold and T. B. Friedman (J. Pediat. 7:768 (Dec.) 1935) that allergic manifestations within the

lungs may simulate infections in the same sense that symptoms due to allergy of the upper respiratory tract may simulate infections of this region. They suggest the term "*allergic bronchopneumonia*" for this clinical syndrome. They present 11 cases of pulmonary allergy which had been variously diagnosed as asthmatic bronchitis, recurrent bronchitis, bronchial pneumonia, recurrent bronchial pneumonia, abortive bronchial pneumonia, nontuberculous pulmonary infection, tuberculosis, perifocal tuberculosis, bronchiectasis, pulmonary abscess, and foreign bodies. Figure 3 illustrates the sequence of events in a typical case. Feingold and Friedman contend that the pulmonary changes are the result of allergic phenomena, resulting in either bronchial obstruction or allergic parenchymal infiltration, or a combination of the two. The specific cause is exposure to a protein substance to which the person is sensitive. It is presumed that infections are not responsible for the symptoms observed. They do not believe that the association of fever is necessarily a manifestation of infection and point out that other allergic conditions do produce a febrile response.

The *prognosis* is dependent upon recognition of the allergic nature, so that systematic treatment may be directed against the underlying constitutional disturbance. The course may be shortened by the administration of **epinephrine** which may produce a sudden cessation of symptoms and a critical drop in temperature. Not unusually, however, the acute symptoms are self-limited, leaving a residuum of a more or less severe stage of bronchial asthma.

**PLEURODYNIA.**—J. M. Rector (Am. J. Dis. Child. 50:1095 (Nov.) 1935) points out that since the clinical picture and course of acute epidemic myalgia or pleurodynia may differ in young children from the clinical picture

as usually described for adults, the diagnosis of this disease in children may be overlooked, particularly is this apt to be the case in sporadic instances.

The occurrence of pleurodynia is distinctly seasonal and reaches epidemic

is by droplet infection by way of the nasopharynx. The period of incubation has not been established. Contact cases have been reported after periods varying from 4 to 14 days. There is no age group which is exempt. The condition,

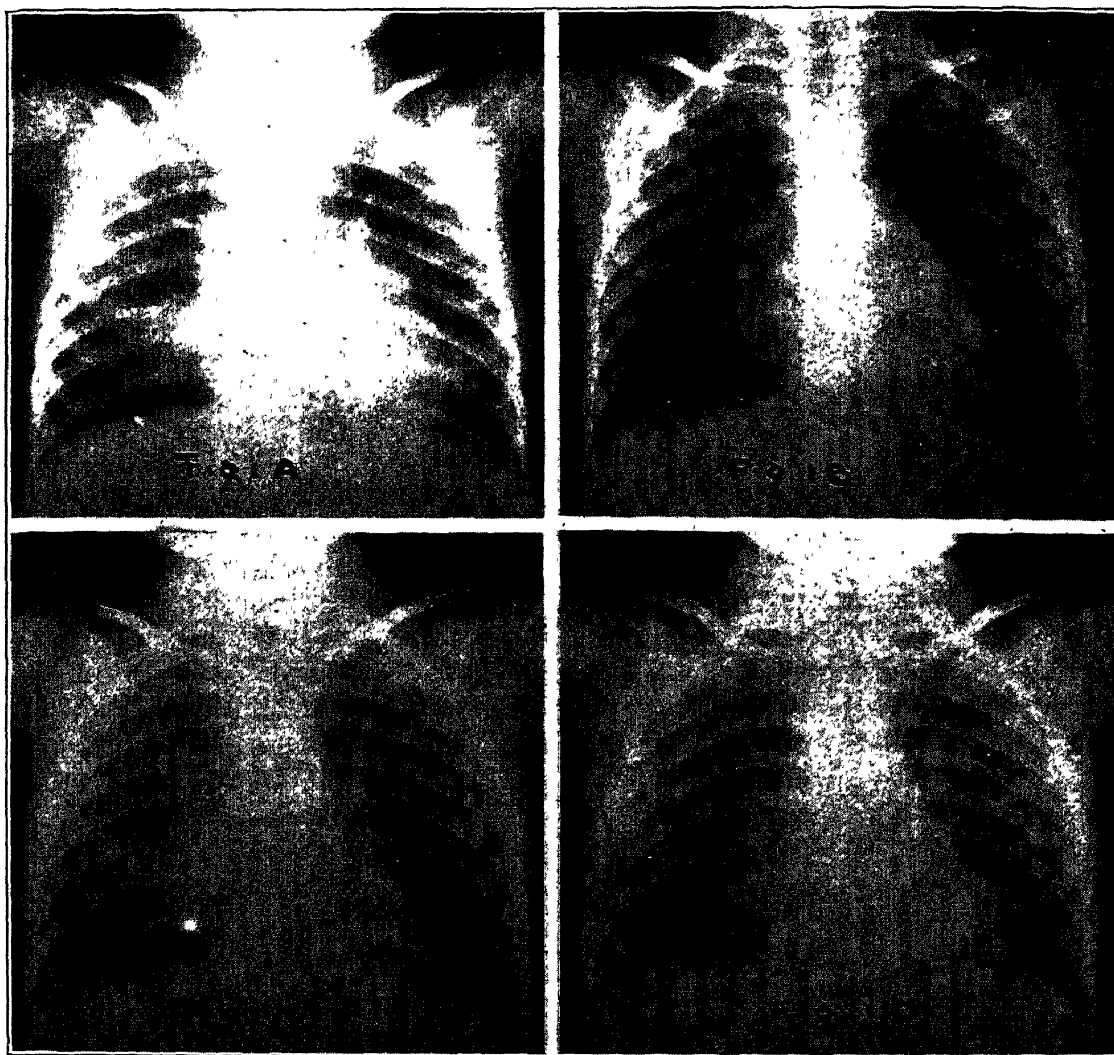


Fig. 3.—Case I. B. O., asthmatic female, aged 5 years. Mantoux (up to 1.0 mg. O. T.) negative. 1A, Taken during asthmatic attack with fever, Jan. 12, 1934. Fan-shaped area of infiltration extending out from each hilus into midlung fields. Diagnosed from film as active tuberculosis. 1B, Taken during period of relative freedom from asthma, Feb. 16, 1934. Marked clearing of previous process. 1C, Taken during recurrence of asthma, March 20, 1934, and showing recurrence of infiltration. 1D, Six weeks later, May 3, 1934, after an interval of freedom from asthma; film shows only hilus thickening characteristic of asthma. (Miller, Piness, Feingold and Friedman: J. Pediat.)

proportions during the summer and fall months, although sporadic cases probably exist throughout the year. The causative agent is not known. It seems most likely that the mode of transfer

however, is uncommon in persons over 25 or 30 years of age and is limited largely to young adults and children. No immunity is conferred by a single attack.

The onset is abrupt, being characterized by severe pain, general malaise and fever. In some instances there may be evidence of a preëxisting infection of the upper respiratory tract. Pain is the outstanding symptom and its distribution is important. Whereas in adults, the pain is chiefly over the thoracic region, in children the pain is largely localized in the abdominal muscles, with little or no thoracic involvement. Anorexia is marked and there may be nausea and vomiting. Some of the older children in the author's series had chills. There are no intrapulmonary findings. The abdominal tenderness is distinctly superficial and there is no true muscular

rigidity, the abdominal findings being similar to those encountered in pneumonia. Recurrent attacks are apparently more common in children than in adults. In 75 per cent. of the author's series there were one or more febrile paroxysms which usually occurred after a symptom-free period of from 2 to 3 days.

No specific treatment of this disease is known. The treatment is entirely symptomatic. In two instances the author observed relief of symptoms after the administration of quinine sulphate. However, it must be borne in mind that this disease is self-limited and is of short duration.

## RUBELLA (GERMAN MEASLES)

By ROBERT A. LYON, A.B., A.M., M.D.

**Diagnosis.**—The *Schilling differential blood count* is a valuable aid in the differential diagnosis of rubella, according to C. M. MacBryde and C. M. Charles (Arch. Int. Med. 56:935 (Nov.) 1935). In a series of 30 patients with uncomplicated German measles they found that the average number of white cells was 5000 per c.mm. at the onset, followed by a gradual rise until normal figures were reached on about the eighth day of the disease. There was a slight rise in the relative number of neutrophils until they constituted about 60 per cent. of the total count, but as the fever and rash subsided, which was usually the fourth day of the disease, the total neutrophil count decreased to about 48 per cent. of the total. The number of stab forms of neutrophils rose rapidly at the onset of the illness and then decreased to normal figures by the eighth to the twelfth day. The eosinophils were normal in number at the onset but tended to increase in percentage, sometimes as many as 10 per cent. on the third to

sixth day of the disease. Lymphocytes and monocytes increased in number from the first to the fourth day and then tended to decrease to normal. Age differences in patients did not seem to influence the reaction of the blood cells.

The blood picture in rubella was found to be different from other diseases. In regular measles there was less of a tendency towards leukopenia and relatively larger numbers of neutrophils, stab cells and juvenile forms, but fewer lymphocytes than in rubella. In scarlet fever the differences were even more marked because of the very high leukocyte count and a large number of neutrophils with relatively large numbers of stab cells and juvenile forms, while the lymphocytes were relatively low in percentage, 14 per cent. or less in many cases. In the drug or toxic rashes, the total leukocyte counts were usually elevated with a relative increase in the numbers of eosinophils and a slight rise in the number of neutrophils and stab cells. If any confusion arose in a single

examination of the blood, serial counts were thought to be definitely valuable in establishing a differential diagnosis between rubella and the other diseases resembling it clinically.

**Complications.**—*Encephalitis* has been observed with increasing frequency as a complication of several acute infectious diseases. Not until recent years has it been reported in association with German measles. Within the past year, a form of encephalitis following German measles was observed in a boy 10 years of age by H. O. Skinner (J. A. M. A. 105:24 (July 6) 1935). Three days after the onset of the German measles, the patient became irritable, lost his appetite and slept a great deal. The next day he suddenly became unconscious, the pupillary reflexes were inactive, the superficial reflexes were absent and the Babinski sign was positive. The cerebrospinal fluid was examined on the following day and found to be under moderately increased pressure and to contain 13 cells per c.mm. Within the next 4 or 5 days the child made a gradual and complete recovery.

Two patients who developed *meningo-encephalitis* following German measles were reported by J. F. Briggs (J. Pediat. 7:609 (Nov.) 1935). The symptoms

of the central nervous system developed 2 days after the onset of the rash. One patient, 10 years of age, died within 24 hours after the onset of the complication and the other patient, 3 years of age, recovered entirely. It was the author's opinion that complications of this nature are not uncommon in severe epidemics of German measles.

**Prevention.**—If German measles is prone to become severe during large epidemics, some method of protection for exposed patients is highly desirable. **Placental extract** was employed recently in the control of an epidemic of German measles by J. Gottlieb (Maine M. J. 27:10 (Jan.) 1936.) Four c.c. were given intramuscularly to 16 nurses and 0.2 c.c. were given intradermally to 46 of the personnel of the local hospital who were exposed to the disease. None of these patients had had the disease previously and none contracted the illness from this exposure. Nine other persons who were in contact with the disease but were untreated, contracted the illness. Reactions to the intramuscular injections were local only and consisted of soreness which lasted for 1 to 3 days. The intradermal injections caused local areas of erythema measuring 2 to 10 cm. in diameter.

## SCARLET FEVER

By JOSEF WARKANY, M.D.

**Etiology.**—On the basis of a study of the records of scarlet fever, measles and whooping cough in the Los Angeles County Health Department area from 1925 to 1934, H. O. Swartout (Am. J. Pub. Health 25:907 (Aug.) 1935) concludes that *climate* and *season* have considerable influence on the incidence of the diseases. Exposure by personal contact may play a greater rôle in the incidence of scarlet fever than would be

expected. The mortality for all 3 diseases has been very low, and they are apparently not as great a menace to life in a subtropical area as they are in colder regions. The streptococci that cause scarlet fever do not appear to be growing less virulent in the Los Angeles County Health Department area.

D. Seegal, B. C. Seegal and E. L. Jost (Am. J. M. Sc. 190:383 (Sept.) 1935) have made a comparative study



of the *geographical distribution* in North America of acute glomerulonephritis, rheumatic fever and scarlet fever. They found that the case rate for scarlet fever diminished progressively from the region between 50° to 45° of latitude to that of 34° to 29°. For rheumatic fever a similar decrease was observed in the same latitudes. In contrast, the yearly hospital medical admission rate for acute glomerulonephritis did not vary significantly in the four regions studied. This contrast might be interpreted as supporting the hypothesis that agents other than the hemolytic streptococcus play the chief etiologic rôle in glomerulonephritis.

**Pathology.**—Studies of the visceral pathology in scarlet fever have been reported by H. Brody and L. W. Smith (Am. J. Path. 12:373 (May) 1936). The underlying *lesion* was found to be one of vascular injury with a concurrent, perivascular round cell infiltration in the heart, liver, kidneys, adrenals and spleen and to a variable degree in the other viscera, including the pituitary, lung, pancreas, and even the testis. The evidence suggests that these lesions are the result of a circulating toxin.

E. Stoeber (Arch. f. Kinderh. 105:193, 1935) has made a pathologic-anatomic study of scarlet fever *myocarditis*. In the heart were found perivascular or interstitial cellular proliferations, which consisted of fibrocytes, histiocytes, plasma cells and leukocytes. There was general cellular enlargement of the endocardium, but no destruction of the vessels or of the rheumatic nodules. The author believes that the findings in the heart cannot be considered Aschoff's nodules. Cellular infiltration and hemorrhages into the bundle of His may be the cause of the sudden death from heart failure.

**Diagnosis.**—A method of early diagnosis is described by I. S. Barksdale,

R. M. Pollitzer and F. P. Simpson (Arch. Pediat. 52:633 (Sept.) 1935). The technic of *culturing the streptococci* is described in detail and they are identified as streptococci scarlatinae by agglutination and lysis. A positive diagnosis is made on the basis of the clumping of large streptococci in the presence of the Schultz-Charlton serum or by actual destruction by lysin. A case of scarlet fever in a 2-year-old child is reported in which the value of this method of diagnosis is shown.

H. J. Gibson and W. A. R. Thomson (Arch. Dis. Childhood 10:429 (Dec.) 1935) report the results of *skin tests with the Dick reagents* and *hemolytic streptococcic extracts* as well as of simultaneous throat cultures in 586 individuals. They did not find any correlation between the incidence of hemolytic streptococcus in the throat and the results of the skin reactions to its products. Repeated tests with Dick toxin and bacterial extract in the same patient revealed a marked variability in the skin reaction to the reagents used. This could not be related to the clinical condition of the patient nor to the presence of hemolytic streptococci in the throat. Dick toxin and Dick control reactions did not run parallel in their fluctuations, with the result that the patient might present what appeared to be a true Dick negative reaction, a positive and a pseudoreaction on consecutive tests. Intramuscular injection of extract did not produce local, focal or general reactions and did not appear to influence the skin reaction. In a certain number of cases neutralization of the reaction to bacterial extract could be produced by an antiserum prepared by immunizing an animal with extract. The skin reacting principle in extracts seemed to be thermostable.

M. L. Spivek (Am. J. Dis. Child. 50:1113 (Nov.) 1935) has made a com-

parison of reactions to *intracutaneous* and *subcutaneous injections of Dick test toxin* in 653 children. Intracutaneous and subcutaneous injections of 0.1 c.c. of toxin for the Dick test, each performed in duplicate, gave identical reactions in 636 of 653 children. The reactions obtained in 17 tests did not agree. Of these, there were 14 positive reactions to subcutaneous injections and 3 to intracutaneous injections, with negative reactions in the duplicate tests. The degree of erythema noted was the same in all but 6 instances.

In a study of the *variability of toxin used for the Dick test*, E. Friedman, A. L. Esserman and M. M. Ginsburg (J. A. M. A. 105:956 (Sept 21) 1935) have come to the following conclusion: There is too great a variability in potency of the Dick toxin available at present to make it serve as a dependable index to the presence or absence of immunity to scarlet fever. Until this toxin is properly standardized and all commercial toxins are of uniform strength, it is impossible to determine with any degree of accuracy to what extent attempts at active immunization have been successful. It would appear that the present scheme of active immunization against scarlet fever rests upon an insecure foundation.

**Surgical Scarlet Fever.**—A general review of surgical scarlet fever has been made by J. Comby (Arch. de méd. d. enf. 38:555 (Sept.) 1935). In his study of surgical scarlet fever F. Karlström (Acta pædiat. 18:287, 1936) reports that the incubation time is rather short—in about 25 per cent. of the cases 48 hours or less. The risk of surgical scarlet fever is probably greater after burns, but is not increased by operations on the throat. At the onset of the disease hemolytic streptococci are found in the throat less frequently than in the usual type of scarlet fever, and in the

terminal stages are equally numerous in the 2 groups of diseases. In surgical scarlet fever they are found more often in the wounds than in the throat. Angina as a primary symptom is not so common. Complications and recurrences are just as frequent in surgical scarlet fever as in the usual type.

**Complications.**—The incidence of *conjunctivitis* as a complication of scarlet fever is reviewed by H. Otto (München. med. Wchnschr. 82:1987 (Dec. 13) 1935). It was found in 5.8 per cent. of 891 cases of scarlet fever and can occur as an early complication between the first and sixth days or as a late complication between the fifteenth and fiftieth days of the disease. The author considers it a toxic allergic reaction.

H. J. Williams (Ann. Otol. Rhin. and Laryng. 44:110 (Mar.) 1935) has presented statistics concerning 2898 patients with scarlet fever complicated by acute suppurative otitis media and 48 patients with a complication of orbital cellulitis. He recommends as useful principles for treatment of *suppurative otitis media*: (1) prevention by keeping the nose and pharynx free from excessive secretions; (2) frequent inspection of the ears, with early myringotomy in every case of bulging tympanic membrane before it ruptures; (3) frequent cleansing of the external auditory canal to facilitate drainage; (4) considering the removal of the adenoids when the ear has discharged for 3 weeks; and (5) performing a simple mastoidectomy on those cases where there is a persistent, profuse otorrhea, sagging of the posterior superior canal, nipple-shaped perforation, mastoid tenderness and edema with fever, and positive x-ray diagnosis of surgical mastoiditis. In *orbital cellulitis* 3 stages can be distinguished: (1) inflammatory edema with or without discoloration of the lids, usually most

marked in the upper lid; (2) edema of the lids with exophthalmos and with or without limitation of orbital movement; (3) same as the second stage, but with evidence of abscess formation. The treatment of the first 2 stages is conservative. Operative procedures are recommended in the third stage.

*Purulent meningitis* during scarlet fever is reported by H. Zischinsky (München. med. Wchnschr. 82:2028 (Dec. 20) 1935). This form of meningitis is rare, 6 instances being observed in 20,000 cases of scarlet fever. The best known form is that following an ear complication. In other cases *metastatic meningitis* is seen. Differentiation between the two forms is not always easy, but metastatic meningitis is apparently more frequent in children than the otogenous type. J. Olmer and M. Legré (Bull. et. mém. Soc. méd. d. hôp. de. Paris 52:422 (Mar. 23) 1936) have described a case of *lymphocytic meningitis* in the course of scarlet fever. The meningitis began on the sixth day of the disease with a sudden elevation of temperature. This complication was not due to a purulent focus of infection and could not be considered a complication of an ear infection. The patient made a complete recovery.

A case of *peritonitis* in scarlet fever is reported by N. Vucetic (Wien. klin. Wchnschr. 48:1163 (Sept. 20) 1935). In a girl, aged 8½ years, the symptoms of peritonitis were observed from the twenty-second day of the disease. Conservative treatment only was used for 4 weeks. Finally, spontaneous perforation took place in the region of the umbilicus, and the child recovered completely.

E. Moro (Ztschr. f. Kinderh. 57:321, 1935) has described a case of *erythema nodosum* in scarlet fever. In a 5-year-old boy scarlet fever developed after adenotomy. Typical erythema nodosum

was seen on the sixteenth day of the disease. The tuberculin reaction was negative as were 9 subsequent tuberculin tests. This case is reported as evidence that erythema nodosum is not always due to tuberculosis. Generally this complicating condition does not develop until the third or fourth weeks of scarlet fever, i. e., in the critical period in which other complications are found.

A study of *gangrene* in scarlet fever and diphtheria has been made by K. Blumberger (Arch. f. Kinderh. 107:154, 1936). Emboli, thrombosis, toxic injuries of the capillaries or injuries of the skin itself may be the pathologic-anatomic basis of the gangrene. It occurs in the third or fourth weeks after scarlet fever. The author has observed gangrene of the left leg caused by an embolus in the popliteal artery.

J. E. Morrish (Lancet 1:949 (Apr. 25) 1936) has described a fatal case of *toxic purpura hemorrhagica* complicating scarlet fever. This case was unusual, since the complication was seen as late as the fourteenth day and in spite of early treatment with scarlet fever antitoxin.

**Epidemiology.**—Recent experiences with *scarlet fever control* have been reported by J. P. Koehler (Am. J. Pub. Health 25:1359 (Dec.) 1935). He finds immunization against scarlet fever with 5 doses of **Dick scarlet fever toxin** both effective and safe. Even children having only 2 doses had a case rate of 15 per 1000 as compared to 60 per 1000 for nonimmunized school children. Nose and throat cultures for the control of scarlet fever carriers may prevent some exposure and infection in spite of the many uncertainties of this procedure. Strict quarantine prevents neither endemics nor epidemics, as too many patients remain carriers after release from the quarantine. Absolute

quarantine of the entire family is probably responsible for more additional cases than the proper isolation of the patient only. Scarlet fever quarantine is based more on tradition and expediency than on scientific fact. Isolation of all children under 7 years of age for 6 weeks during a scarlet fever epidemic reduces the number of cases of the disease and aids in the control of other contagious diseases of childhood.

H. S. Diehl and R. G. Hinckley (J. A. M. A. 106:1354 (Apr. 18) 1936) have discussed the results with scarlet fever immunization during a school epidemic. Their conclusions are as follows: When active and passive immunization procedures were utilized in an attempt to control an epidemic of scarlet fever among 436 students of an agricultural school, the number of new cases declined abruptly after the administration of the third dose of scarlet fever toxin. A large proportion of the individuals had mild reactions to the toxin and approximately 5 per cent. of the group were admitted to the infirmary after each injection. These reactions were of short duration and not serious but, when accompanied by a rash, introduced difficulties into the diagnosis. Ninety-three per cent. of a group of susceptible students who had received more than 11,000 skin test doses of scarlet fever toxin showed negative Dick tests 6 months later. Thirty-eight per cent. of 23 other individuals, who had had positive Dick tests at the time of the epidemic but had received no toxin, gave negative tests 6 months later. Scarlet fever antitoxin was administered prophylactically to 25 susceptible individuals who had been in close contact with patients with scarlet fever. Seventy-six per cent. of these had serum reactions and 68 per cent. moderately severe or very severe reactions. Five of the group, who received scarlet fever anti-

toxin prophylactically, developed scarlet fever. The therapeutic results obtained with the scarlet fever antitoxin were satisfactory in this small series of patients.

**Prophylaxis.—Active Immunization.** An analysis of the results of methods of immunization against scarlet fever has been made by G. W. Anderson and W. I. Reinhardt (J. Infect. Dis. 57:136 (Sept.-Oct.) 1935). These authors conclude that the *Dick test*, as it is employed under a variety of conditions by many individuals and with the solutions commercially available, is a reliable index of immunity to scarlet fever. Five injections of **Dick toxin** confer an immunity comparable to that indicated by a negative Dick test. This immunity lasts at least 3 years. Contact with cases of scarlet fever does not increase the hazard of contracting the disease, provided the individuals had previously been immunized with the Dick toxin. Although the principal disadvantage of the toxin is the severity of the reaction that it occasionally produces, these are never serious and do not constitute an excuse for failure to immunize those unduly exposed to the disease. Hospitals can eliminate scarlet fever in the nursing staff through routine immunization of all nurses found by the Dick test to be susceptible. The authors recommend that scarlet fever immunization of the nursing staff be made a routine practice in all hospitals, especially in those handling children.

A study of active immunization against scarlet fever in charitable institutions and the public schools of Philadelphia has been made by J. N. Henry (J. A. M. A. 105:488 (Aug. 17) 1935), who concludes that immunization against scarlet fever should be much more widely adopted and vigorously advocated by physicians than is done at present. The proper administra-

tion of the toxin and a most careful reading of the test within the specified time are fundamental. The education of the parents is of the utmost importance in obtaining coöperation, and the proper care of the child for a period of 6 hours after each injection will greatly lessen the incidence and severity of the reaction. The author believes that scarlet fever can be eliminated as a serious private and public health problem by this prophylactic method.

The advantages of a purified and concentrated toxin for skin testing and immunologic purposes are pointed out by G. F. Dick and A. K. Boor (J. Infect. Dis. 57:164 (Sept.-Oct.) 1935). A purified and concentrated scarlatinal toxin, containing 20,000,000 or more skin test doses per gram and of low nitrogen content, has been prepared by a combination of fractional precipitation with ammonium sulphate, treatment with an aluminum hydroxide preparation, dialysis and evaporation.

B. Rappaport (J. A. M. A. 106:1076 (Mar. 28) 1936) believes that by means of a more gradual approach to the final dose of 80,000 skin test doses, the active immunization with scarlet fever streptococcus toxin can be accomplished with a marked reduction in the number and severity of the reactions.

R. J. Reid (New York State J. Med. 36:403 (Mar. 15) 1936) has found that the raw toxin of streptococcus scarlatinae can be modified by oxygenation, and still retain its immune-producing powers. This toxin produces immunity in the greater number of individuals upon the initial retest, but the percentage undergoes a sharp decrease over a period of 6 months. Modified toxins can be given in greater concentration over a shorter period than raw toxins and produce a comparable percentage of immune individuals. Over a period of 6 months the percentage de-

crease is much less than with raw toxin and a greater number of individuals not immune upon the initial retest will develop immunity over a period of 6 months as compared with susceptible persons who have received raw toxin. Raw toxin produces some general reactions but few local ones, while modified toxins cause some severe local and general reactions.

W. Heesen and B. Rückert (München. med. Wchnschr. 82:1838 (Nov. 15) 1935) recommend the use of **Gabritshewsky vaccine** as a protection against the transmission of scarlet fever. This vaccine is a culture of streptococci scarlatinae treated with formaldehyde. A single injection of 1 c.c. was administered intramuscularly. No serious reactions were observed.

A study of scarlet fever immunization by inunction has been made by M. L. Ripps (J. Pediat. 7:754 (Dec.) 1935). The preparation and administration of the inunction is described. Of a total of 142 Dick positive children who were treated with inunctions of scarlet fever toxin, 62 became negative to the Dick test. Cold cream inunction proved superior to lanolin, because it was more pleasant to handle, was more quickly absorbed, and resulted in a higher percentage of immunizations. Those giving the most marked reactions to the Dick test were the most difficult to immunize. The results were very poor in children from 1 to 4 years of age, in spite of the larger doses given. Increasing the dosage was of no value in increasing the number of immunizations. All those who became negative to the Dick test did so within the first 6 weeks. Retests after 1 and 1½ years differed very little from the earlier tests. Of 38 children who were negative at 6 weeks only 1 had become positive 1 and 1½ years later. The author concludes that the inunction method of immunization

is of little apparent value in children with a marked Dick reaction. Only about 20 per cent. became negative. It is probable that owing to constant minimal exposure, some of these would have become negative without treatment.

*Passive Immunization.*—C. F. McKhann, A. A. Green, L. E. Eckles and J. A. V. Davies (Ann. Int. Med. 9:388 (Oct.) 1935) have found that protein extracts of the globulins derived from the human placenta contain scarlet fever as well as other antitoxins. In a study on the effectiveness of placental extract by oral administration they have found that 22 children with positive Dick reactions were rendered Dick negative by the oral administration of the extract in cold water on an empty stomach. Duration of the negative phase varied, but could be prolonged up to 18 days if iced alkaline carbonated water was used as a vehicle. Reversal of the Dick test could not be obtained with any regularity in adults.

*Treatment.*—The use of convalescent scarlet fever serum for prophylactic and therapeutic purposes is advocated by A. L. Hoyne, S. O. Levinson and W. Thalhimier (J. A. M. A. 105:783 (Sept. 7) 1935). The dose

employed for prophylaxis was 10 c.c. in children under 10 years of age and 20 c.c. for those over this age. Scarlet fever did not develop in 97.2 per cent. of 862 home contacts without a history of scarlet fever, who were immunized passively with convalescent scarlet fever serum; nor did it develop in 95 per cent. of 83 Dick positive hospital contacts immunized with the serum. The disease was usually seen in a modified form in immunized contacts in whom it did develop. The authors state that convalescent scarlet fever serum in adequate therapeutic doses (20 c.c. to 100 c.c.) may abort the disease, usually caused regression of fever, diminution of toxemia and angina, fading of the rash, and appreciably shortened the period of illness. It also prevented the development of complications or reduced the frequency of their occurrence. The influence of serum on late and complicated cases was less marked, but frequently seemed beneficial. By reducing the severity of the disease and the incidence of complications, the mortality rate was definitely diminished. No unfavorable reactions were observed after the administration of human convalescent scarlet fever serum.

## SMALLPOX

By ROBERT A. LYON, A.B., A.M., M.D.

### SMALLPOX VACCINATION.—

It is possible to separate from vaccine lymph certain elementary bodies described originally by Paschen. Employing the Craigie method, R. F. Parker and T. M. Rivers (J. Exper. Med. 62:65 (July) 1935) obtained a preparation of relatively pure elementary bodies which had a high vaccine virus titer and could be agglutinated by the serum of a rabbit immunized with vaccine virus. Similar results have been obtained by

M. H. Finlayson (Brit. J. Exper. Path. 16:358 (Aug.) 1935). The exact nature of these elementary bodies is not known definitely but they seemed to be closely associated with the virus itself.

Use has been made of culture vaccine virus in the immunization of infants and children against smallpox by T. M. Rivers and S. M. Ward (J. Exper. Med. 62:549 (Oct.) 1935). The strain of vaccine virus employed had been grown on a medium of chick embryo tissue

suspended in Tyrode's solution and has been carried through 130 successive passages over a period of 3 years. During that time the potency of the vaccine virus was shown to be maintained, and the material could be dried and sealed in ampules without losing its activity for a long period of time. For use, the dried virus is suspended in saline solution and inoculated intradermally in doses of 0.1 c.c.

*Generalized vaccinia* contracted from a vaccination take of a sister was reported in an infant 1 year of age by D. J. Bradley (J. Med. 17:14 (Mar.) 1936). The infant had had an eczema for several months previously. The vaccinia covered the cheeks, the legs and forearms and was followed by inguinal adenitis which required drainage. Recovery was complete, without permanent scarring.

## CONGENITAL SYPHILIS

By ROBERT A. LYON, A.B., A.M., M.D.

**Diagnosis.**—The value of the *x-rays* in diagnosing syphilis in the early days of an infant's life has been studied recently by N. R. Ingraham, Jr. (Am. J. Dis. Child. 50:1444 (Dec.) 1935). In a series of more than 1500 babies discharged alive from the obstetrical division of the hospital, there were about 12 per cent. whose mothers had a history of syphilis. Not one of the newborn infants whose mothers had syphilis showed any clinical evidence of the disease. The Wassermann reaction gave evidence of syphilis in only 9 infants of the total of 195 offsprings of syphilitic mothers. By means of the *x-rays*, 26 additional patients, or 19 per cent. of the total group, were diagnosed as having lues before the age of 6 days, and 23 other patients, or 17 per cent. were diagnosed by that means between the ages of 1 and 10 months. All of this group of infants had positive serologic reactions later in life. In the case of the infants whose mothers had had some treatment during the prenatal period, the *x-ray* evidence of the disease was found in a smaller percentage. Of 36 patients who had no *x-ray* evidence of the disease at the age of 6 days, one-third of the group developed syphilitic bone changes when they were 3 to 6 months old.

Further observations regarding the time at which the first *x-ray* changes occurred in the *bones* of the newborn infants infected with syphilis were reported by N. R. Ingraham, Jr. (Am. J. M. Sc. 191:819 (June) 1936). A group of 131 infants born of syphilitic mothers were studied with serial *x-ray* pictures to determine the time at which osteochondritis could first be noticed. Of a group of 7 babies whose mothers had had signs of secondary syphilis more than 23 weeks previously, all showed *x-ray* evidence of syphilitic osteochondritis at the first examination shortly after birth. Periostitis did not occur until several months after *x-ray* evidence of osteochondritis was noted. From these studies the author concluded that a period of at least 5 weeks was necessary from the time of infection until signs of osteochondritis could be found in the *x-ray* picture, and syphilitic periostitis required approximately 4 months to be detected by the same method. If only 1 *x-ray* picture were taken of an infant, the author recommended that it be done when the patient was 6 weeks old, because any evidence of syphilis could be detected at that time.

Congenital syphilis seems to hasten the appearance of *epiphyses* and *ossification*

centers in the x-ray pictures of infants and children. J. Signorelli, H. Hosen and J. M. Miles (J. Pediat. 7:182 (Aug.) 1935) examined the x-ray pictures of 71 infants with congenital syphilis and found that 28 showed an early appearance of these centers and 43 were normal. Similar findings were noted in the x-ray films of children with rickets so that the authors concluded that these 2 diseases should not be held accountable for retarded development of ossification in infants and children.

Another *osseous change* which is thought to occur only in patients with congenital syphilis is the *enlargement of the sternal end of the clavicle*, first described in 1930 by G. K. Higoumenakis (Deutsche Ztschr. f. Nervenhe. 114:288, 1930), who noticed it in 170 patients and thought it one of the most frequently occurring signs of congenital syphilis. It has been verified in a series of 12 patients who had congenital syphilis by M. Dorne and S. J. Zakon (Arch. Dermat. and Syph. 32:602 (Oct.) 1935). It most frequently occurs as an enlargement of the sternal end of the clavicle on the right side, although occasionally it has been noted on the left side in patients who are left-handed. The lesion consists of an osteochondritis, which was thought to be augmented by the constant friction of the clavicle against the sternum and, therefore, was observed more frequently in the older children and young adults than in younger patients.

The diagnosis of congenital syphilis by *dark-field examination of scrapings from the umbilical vein* has been found to be possible by N. R. Ingraham, Jr. (J. A. M. A. 105:560 (Aug. 24) 1935). With this method spirochetes were found in 25 of a group of 95 infants delivered of syphilitic mothers. Six of these infants were stillborn and 19 were living infants who had no clinical symptoms of the disease at the time of birth, although all

subsequently developed other evidence of syphilis. Of the 35 infants in whom no spirochetes were found by the dark-field examination, 54 per cent. later developed signs of syphilis. The value of the procedure of examining the umbilical vein was thought to be the early diagnosis which was possible in a limited number of infants. Negative results did not rule out the disease, and other methods of diagnosis were necessary for such cases. The technic of the dark-field examination consisted in cutting a portion of the umbilical cord about 3 inches in length and placing it in a sterile moist bottle until the microscopic examination is made, which should not be longer than 8 hours after the specimen is obtained. The distal ends of the section of cord were cut off and discarded, and in the middle inch the vein was identified and a probe inserted into it. A sharp scalpel was employed to cut down through the cord on to the probe, the blood was scraped off of the vein, the knife wiped clean and additional scrapings placed in physiologic salt solution, macerated and examined with the dark-field microscope.

The value of *quantitative Wassermann tests* in making an accurate diagnosis of early congenital syphilis has been stressed by H. K. Faber and W. C. Black (Am. J. Dis. Child. 51:1257 (June) 1936). Many infants at birth have positive Wassermann tests without the syphilitic infection, probably because antibodies had been transferred by the mother to the infant. Fildes is quoted as saying that "the Wassermann reaction of cord blood is diagnostic of syphilis in the mother rather than in the child." With this fact in mind, the authors have made quantitative Wassermann tests with various dilutions of serum. In 10 infants in which the Wassermann reaction was positive shortly after birth, quantitative tests showed that the reagin disappeared from the blood rapidly and frequently was



gone by the seventh day, although it did not reach zero in one instance until the ninety-fourth day. By the ordinary qualitative Wassermann test, however, the change from positive to negative often did not occur until quite a bit later in the child's life, and strongly positive reactions were frequently observed as late as the fifty-second to the seventy-third day. It was concluded that many infants with positive Wassermann reactions did not need to be subjected to the antisyphilitic treatment providing the quantitative Wassermann test showed the rapid disappearance of antibodies from the blood serum. It was suggested that the transmission of syphilitic reagin from the mother to the fetus without the transmission of syphilis itself should be considered as Fildes' law.

The value of several different methods of diagnosis of infantile congenital syphilis has been reviewed by N. R. Ingraham, Jr. (Am. J. Syph. and Neurol. 19: 547 (Oct.) 1935), who showed that about 50 per cent. of the infants born of syphilitic mothers developed the disease. The chances of an untreated syphilitic mother having a diseased child were about 80 per cent., while mothers who had been treated for the last 5 months of their pregnancy rarely had syphilitic children. The problem, therefore, is the early diagnosis of the disease in the infant. The clinical history and physical examination will arouse suspicion of the disease in about 80 per cent. of instances, but clinical manifestations of syphilis in the newborn are rarely present. The Wassermann reactions are not reliable in many infants of this age, and even a negative Wassermann in a mother who has had syphilis is not absolute proof that the child will be free from the infection. The additional diagnostic methods which the author recommends for the detection of lues in the newborn are (1) the *dark-field examination of the umbil-*

*ical vein for spirochetes*, which may be found in about 20 per cent. of infants with syphilitic mothers; and (2) the *x-ray examination of the long bones*, which will usually show syphilitic involvement in about 30 per cent. of instances. It was the conclusion that a combination of these methods will lead to a diagnosis of syphilis in about three-fourths of the average group of newborn infants before they are 2 months of age.

**Treatment.**—The results of the treatment of 279 infants 2 years of age or younger have been summarized recently by F. R. Smith, Jr. (*Ibid.* 19: 532 (Oct.) 1935). About 83 per cent. of the group were admitted to the clinic before they were 6 months of age and by that time all but 20 per cent. had some active lesions of syphilis. Seventeen per cent. of the infants less than 3 months of age died before or shortly after treatment was instituted. Of the entire number of fatalities of the group, syphilis was the direct cause of death in about 36 per cent., and 91 per cent. of these deaths occurred in children less than 6 months of age. The infants whose mothers had had at least 9 antisyphilitic treatments during the prenatal period rarely had active lesions of syphilis, and only about 5 per cent. of this group became Wassermann-fast as contrasted with about 24 per cent. of the group as a whole. Persistently positive Wassermann reactions were much more frequent in children who had not received sufficient treatment, but the most important factor in causing this condition seemed to be the delay in starting treatment until later in life.

The number of relapses of the disease increased rapidly as the age of the children increased but those who had received adequate early treatment rarely had relapses. Involvement of the central nervous system was found in about one-third of the number of patients examined and was thought to be of less sig-

nificance in infants than in older age groups. The incidence of Hutchinson's teeth later in life was much less in children who had been treated since infancy and this seemed to indicate that adequate treatment might prevent the occurrence of this condition. The author stressed the point that the important factors in the treatment of congenital syphilis are not only the amount and the duration of the treatment but the *time* at which it is instituted. The methods of treatment of congenital syphilis employed by the author consisted of alternating courses of **arsphenamine** and **bismuth** except that in smaller children **sulpharsphenamine** administered intramuscularly was substituted for arsphenamine. Bismuth was employed in the form of 10 per cent. **bismuth salicylate**.

Among 370 children with congenital syphilis who were observed later in life, F. R. Smith, Jr. (*Ibid.* 20:45 (Jan.) 1936), found that 130 had a positive Wassermann test as the only evidence of syphilis, 44 had interstitial keratitis, 36 had central nervous system lesions, 6 had bone lesions, and none had the syphilitic type of deafness. Paroxysmal hemoglobinuria occurred in 6 patients, Hutchinsonian teeth and other "basic stigmata" in 84. Lesions were found in 18.6 per cent. of the syphilitic children 2 to 4 years of age and in 44 per cent. of the older boys and girls. Early and vigorous treatment probably prevented the occurrence of some relapses, but did not delay the age at which they appeared. The later antisiphilitic treatment was begun, the greater was the incidence of Wassermann-fastness in these patients. All of the lesions of congenital syphilis, except those of the central nervous system, yielded readily to the regular methods of treatment.

**Acetarsons** (**stovarsol**) for the oral treatment of patients with congenital syphilis has been highly recommended by

A. S. Traisman (*J. Pediat.* 7:495 (Oct.) 1935). Over a period of 3 years 65 patients have been treated with this form of therapy following the Bratusch-Marrain technic. Twenty-one of the group were infants under 1 year of age who received from 1 to 7 courses of acetarsone. A total of 17 became serologically negative, and of the 4 who remained positive, only 1 had had adequate treatment. Twenty-two children between the ages of 1 and 6 years received from 1 to 8 courses of treatment, but only 12 of the group had had 3 courses or more and about 40 per cent. of the group became negative serologically. Of the 22 older children, between 6 and 12 years of age, 27 per cent. developed reversals of their serologic tests. Attendance at the clinics by the older children was irregular.

The effect of the acetarsone in healing syphilitic bone lesions was found to be satisfactory. X-rays of 18 infants and children of the above group showed evidence of syphilis in the bones and healing occurred after 1 or 2 courses of the drug. Reactions in these children following the use of acetarsone included the transitory occurrence of albumin and, occasionally, blood and casts in the urine. At any sign of this disturbance or of any other, such as diarrhea, vomiting, and skin eruptions, the author was accustomed to stop all treatment until the patient was entirely well of any disturbance caused by this therapy. The tonic effect of this type of arsenic was noticed in many children. For older patients it was thought advisable to add **bismuth** to the therapeutic schedule.

Another favorable report of **stovarsol** therapy in the treatment of congenital syphilis was made by A. M. Davidson and A. R. Birt (*Canad. M. A. J.* 34:33 (Jan.) 1936). They have administered the drug to a group of 37 children over a period of 2 years or less. The therapy

seemed effective in producing negative Wassermann reactions and its great advantages were the simplicity of administration, the low cost, and its acceptance by the patients with an improved spirit of coöperation. In 3 instances, toxic

symptoms of headache, abdominal pain or diarrhea seemed to be caused by the stovarsol, but in many other cases the tonic effect of the drug in improving the general physical condition of the children was noticeable.

## TUBERCULOSIS IN CHILDREN

By WALDO E. NELSON, A.B., M.D.

**Pathogenesis.**—An x-ray lesion, quite like that of so-called *epituberculosis*, or benign resolving primary pulmonary tuberculosis, has been produced experimentally by E. H. Oppenheimer (Bull. Johns Hopkins Hosp. 57:247 (Nov.) 1935) by introducing dead tubercle bacilli into the bronchus of rabbits hypersensitive to the tubercle bacillus. The resulting lesion, which exhibited the x-ray appearance and clinical course of that in human *epituberculosis*, reached its maximum density in 2 to 4 weeks, and then gradually cleared completely, clearing often beginning at the periphery. No such lesion occurred in nonallergic animals subjected to the same procedure. Immunized hypersensitive animals injected intratracheally with living tubercle bacilli developed a similar shadow, which, however, spread progressively and resulted in a fatal termination. Histologically, the lesion is that of a typical tuberculous pneumonia with epithelioid and giant cells, lymphocytes and caseation. Later, peripheral organization, absorption of the exudate and nonspecific scar formation occurred. These observations indicate that the peculiar characteristics of so-called *epituberculosis* can be produced by the discharge of dead bacilli into the lungs of an allergic person by way of a bronchus. It is suggested that the characteristics of *epituberculosis* represent in many, if not in all, cases the results of erosion of a bronchus by a caseous lymph node containing relatively few viable bacilli, and

that the characteristic shadows represent a tuberculous pneumonia produced by the discharge of caseous material impregnated with tuberculo-protein and dead bacilli, though containing some living bacilli, into the lung of a host sensitized and immunized by the previous infection. If a similar accident occurs in the case of a node containing many live bacilli, a shadow of precisely similar form develops, but the process extends progressively.

R. Rössle (Virchow's Arch. f. Path. Anat. 296:1, 1935) also questions the usual explanation that *epituberculosis* represents a so-called circumfocal inflammatory infiltration which may be either tuberculous or nonspecific. He attributes the pulmonary changes to a resorption atelectasis resulting from compression of a bronchus by enlarged caseous lymph nodes. He also recognizes the possibility of erosion of a bronchus by a caseous node. However, he believes that the primary pulmonary change in such an instance is also due to atelectasis, although the atelectatic as well as the nonatelectatic portions of the lung are apt to become infected.

**Vitamin C Deficiency.**—An investigation to determine the rôle of chronic vitamin C deficiency in the pathogenesis of tuberculosis in the guinea-pig has been conducted by M. R. Greene, M. Steiner and B. Kramer (Am. Rev. Tuberc. 33: 585 (May) 1936). They found that chronic vitamin C deficiency combined

with a progressive tuberculous infection caused a significant shortening of the survival period and a significant decrease in body weight of guinea-pigs. While chronic scurvy was not instrumental in the development of generalized tuberculosis in animals infected with the relatively avirulent strain, R. 1, generalized tuberculosis did develop more rapidly in chronic vitamin C deficient animals than in nonscorbutic animals when infected by the subcutaneous or enteric route with strain H 37, or with tuberculous sputum. Guinea-pigs maintained on a partially depleted vitamin C diet developed more lesions and ulcers in the intestinal tract than did animals on a complete diet when fed tubercle bacilli. Animals infected with tuberculosis and allowed to develop acute scurvy did not show more tuberculosis than did the control guinea-pigs.

**Clinical Manifestations.** — *Body Measurements.* — An anthropometric study of tuberculous children has been carried out by H. B. Pryor and H. Mathiasen (*Ibid.* 33: 348 (Mar.) 1936). They found a consistent variation from average toward slender build in 210 tuberculous children when compared with 6000 healthy children of the same ages from the same region. Width-length indices used to classify body build had consistently smaller mean values at all ages from 2 to 16 years and for both sexes in tuberculous groups than in the normal control groups. Head and face measurements were consistently smaller and the necks tended to be longer and of smaller circumferences for the tuberculous children than for the normal population. The preadolescent tuberculous children tended to have barrel-shaped chests compared with the normal controls. There were no consistent differences in height between the tuberculous and nontuberculous children. The tuberculous children were consistently below the controls in weight, but when their

slender body builds were taken into consideration, their relative nutrition was just as good.

*Hematogenous Distribution.* — According to E. M. Lincoln (*Am. J. Dis. Child.* 50: 84 (July) 1935), it is probable that blood stream invasion follows closely primary tuberculous infection in almost all instances. This argument is based on clinical, bacteriologic, and pathologic evidence. The author separates the types of hematogenous distribution into 4 groups, as follows: (1) the protracted form of generalized dissemination; (2) acute generalized miliary tuberculosis; (3) renal or osseous tuberculosis which, while it results from hematogenous distribution, is usually not thought of in those terms; (4) bacilleemia in which there may be no changes evident on physical examination. The end result in the occult cases of bacilleemia may be recognized at times in the x-ray pictures of the lung or, rarely, in the spleen and cervical nodes. The clinical picture which results from marked protracted hematogenous dissemination of tubercle bacilli is said to be a clean cut entity. The most characteristic lesions of this form of tuberculosis at the height of its development are marked panadenitis and panserositis and associated x-ray evidence in the lungs of bilateral, symmetrically distributed nodules, varying from submiliary tubercles to those the size of a half-dollar and of similar lesions in the spleen and other organs. The involvement of the serous surfaces may at times be limited to a clear exudate or to extensive adhesions. In the marked cases, caseation of the serous surface may be present. The tracheobronchial as well as the superficial nodes are markedly enlarged. A mass of inguinal nodes which produced elephantiasis of the leg, as a result of occlusion of the lymphatics, has been observed by the author.

*Calcified Abdominal Nodes.*—A clinical study of 147 children with calcified abdominal lymph nodes has been made by C. A. Smith and F. D. Ames (J. Pediat. 8:205 (Feb.) 1936). From the observations made of this group, it would seem that such nodes are not important foci for the dissemination of tuberculosis to other parts of the body. Active pulmonary tuberculosis did not develop in any of the patients. Associated tuberculous lesions were more commonly non-pulmonary than pulmonary. About one-half of the total group had no symptoms referable to the calcified nodes. In the remainder the usual symptom was prolonged and recurrent abdominal pain was observed. Attempts to correlate the location or extent of the pain with the size, location, degree of calcification, or number of such nodes were not successful. Initial treatments for those children who manifested symptoms consisted of an adequate diet containing pasteurized or boiled milk, exposure to the sun and especially sufficient daily rest to induce the cessation of pain. Of 71 children with symptoms, 57 recovered under general hygienic treatment; 11 continued to have some pain; and 3 were treated surgically with relief. **Surgery** was advised only after the prolonged trial of general symptomatic measures. An example of a calcified abdominal node is shown in Fig. 1.

*Pulmonary Obstruction.*—Several instances of *pulmonary emphysema* resulting from incomplete obstruction of tuberculous origin in a main bronchus are reported by C. A. Faust (Am. J. Dis. Child. 51:118 (Jan.) 1936) and by M. L. Spivek (*Ibid.* 69). The obstruction may be acute or chronic. Spivek reports 4 cases illustrating different types of obstruction. In the first instance, bronchoscopic examination revealed an obstructive deformity of the left main bronchus due to pressure from without, in

all probability from a tuberculous hilar node. Later evidence suggested that this node broke down and ruptured into the bronchus. The results of obstruction following this accident were presumed to be due to a mass of tuberculous granulation tissue at the site of the rupture. In

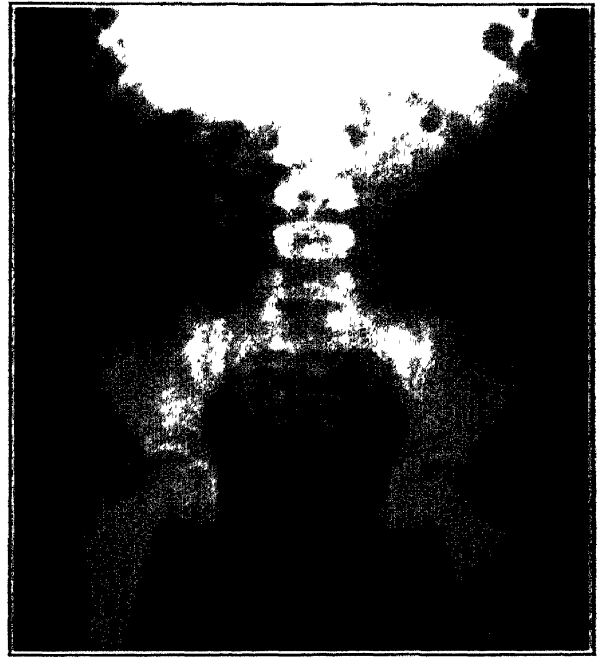


Fig. 1.—Calcified nodes associated with recurrent abdominal pain in a girl six years of age. Relief of symptoms followed symptomatic treatment. (Smith and Ames: J. Pediat.)

Spivek's second case, the obstruction was present only during the period of rupture and discharge of the caseous contents of a tuberculous node. The third patient had an *emphysema* of 2 years' duration which was assumed to be due to a contracture of scar tissue. The fourth patient had a partial obstruction from without by pressure of a tuberculous node. This patient died from tuberculous meningitis.

In Faust's patient there was narrowing, as shown by bronchoscopic examination, of the left main bronchus, probably due to obstruction by tuberculous hilar nodes from without. An obstruction was also shown in the right lower bronchus, due to a growth within the bronchus.

This growth was removed and thought to be tuberculous. Five and a half years later, this boy had no evidence of active tuberculosis.

*Effect of Other Conditions on Tuberculosis.*—An occurrence of *whooping cough* in 7 children with tracheobronchial



Fig. 2.—(Case 1.) Atelectatic pneumonia consolidation, right upper lobe, with shifting of heart, great vessels and trachea to affected side. (Nissler, Sokoloff and Cohen: *Am. Rev. Tuberc.*)

tuberculosis who were patients in a sanatorium is reported by J. I. Hershey and F. Ward (*Am. Rev. Tuberc.* 32:612 (Nov.) 1935). In contrast to the generally accepted view that whooping cough is a grave complication of latent pulmonary tuberculosis, none of these children exhibited any untoward effects, clinically or roentgenographically, from the whooping cough. In fact, the authors seemed to feel that most of them benefited from the enforced bed rest.

*Diabetes.*—In an attempt to throw more light upon the apparent increased susceptibility of diabetics to tuberculosis, M. M. Steinbach, S. J. Klein and M. Deskowitz (*Ibid.* 32:665 (Dec.) 1935)

have studied the effect of tuberculosis in the depancreatized dog. The dog is highly resistant to mammalian tubercle bacilli. The authors found that the human strain of tubercle bacilli, H 37, did not infect the control animals, although large doses were injected intraperitoneally; whereas 6 of the 7 diabetic (pancreatectomized) dogs developed tuberculosis. When a pathogenic bovine strain, B 1, was used, 2 of the 3 control dogs developed tuberculosis, but in contrast all 3 of the pancreatectomized diabetic animals became tuberculous and the disease was always more invasive and involved more organs. The authors concluded that the dog, when rendered diabetic, becomes vastly more susceptible to tubercle bacilli.

Four of 5 pancreatectomized dogs, in which the diabetes was temporary due to regeneration of pancreatic tissue, failed to develop tuberculosis, in spite of the fact that they lost weight and were extremely emaciated before death. From this, the authors argue that the increased susceptibility to the tubercle bacillus was not due to the lack of the pancreatic digestive enzymes and consequent emaciation, but much more likely to faulty carbohydrate metabolism which results from the absence of islet-cell secretion (insulin).

A. L. Newcomb (*Ibid.* 32:507 (Nov.) 1935) reports that 6, or 15 per cent., of 40 diabetic children from 1 to 15 years of age reacted positively to intracutaneous tuberculin skin tests in contrast to 38.6 per cent. in Vienna and 47.7 per cent. in Boston. No case of adult type of tuberculosis or phthisis was found.

*Differential Diagnosis.*—Three instances of nontuberculous pulmonary disease simulating tuberculosis in children are reported by C. W. Nissler, M. J. Sokoloff and L. Cohen (*Ibid.* 32:702 (Dec.) 1935). These cases illustrate that nontuberculous lesions can be located in the upper lobe and can be unilateral. All

three of these children had positive tuberculin skin reactions and x-ray evidence which suggested tuberculosis. The x-ray pictures of the chests of these children are illustrated in Figs. 2, 3 and 4, respectively. The diagnosis from bronchoscopic examination in the first case was *atelectasis* due to bronchial obstruction which was caused by organisms other than the tubercle bacilli. In the

32:257 (Sept., 1935). Although the brucella organism was not isolated either from the blood or from the spinal fluid, it was felt that a brucella infection was the etiologic factor in view of the undulant and irregular type of fever, the mild secondary anemia, the generally low white blood count with a decrease in polymorphonuclears, the marked sweating, the loss of weight, the orchitis,



Fig. 3.—(Case 2.) Congenital cyst of lung. Lipiodol injection in roentgenogram on right. (Nissler, Sokoloff and Cohen: Am. Rev. Tuberc.)

second case the diagnosis was *congenital cyst of the lung* and that of the third case was *pulmonary fibrosis of nontuberculous origin*. Repeated examinations of the sputum and of the contents from gastric lavage by direct smear, cultures and guinea-pig inoculations failed to disclose tubercle bacilli. One factor which the authors considered to be against the diagnosis of tuberculosis in these instances was the long duration without apparent change of the lesions.

*Meningitis*.—An instance of involvement of the spinal meninges and of bone in undulant fever simulating tuberculosis is reported by S. U. Marietta (*Ibid.*

cough with abundant mucopurulent expectoration, the long duration of the disease (2 years and 3 months), the positive agglutinations (1-160 to 1-320), and the apparent elimination of other infectious agents. The possibility of a tuberculous infection, the absence of tuberculous lesions elsewhere in the body, the numerous negative smears and cultures, the radiographic appearance of the bone lesions which was entirely different from that seen in tuberculosis of the bone, showing little of a destructive and much of a regenerative process, and more specifically by the numerous negative animal inoculations.

*Tuberculin.*—Clinical observations to determine the comparative sensitivity of the various types of tuberculin tests continue to be reported. G. Anzén (Am. J. Dis. Child. 50:104 (July) 1935) has compared the intracutaneous or Mantoux test, the cutaneous or Pirquet, and the plaster test in a group of 1838 children.



Fig. 4.—(Case 3.) Shows considerable fibrosis of left upper lobe with cavitations. Mediastinum and trachea are drawn to left. (Nissler, Sokoloff and Cohen. Am. Rev. Tuberc.)

The plaster and the Pirquet tests yielded consistent results in 98 per cent. of the cases. In 0.5 per cent. of the cases, positive reactions were obtained from the plaster test when the reaction to the Pirquet test was entirely negative. In febrile states the plaster test was said to be somewhat more sensitive than the Pirquet test. Those who failed to react to the plaster test were retested by the intracutaneous method and only 1.25 per cent. were found to have positive reactions.

Evidence that *allergy* to the tubercle bacillus, as evidenced by a positive tuberculin skin reaction, may diminish or dis-

appear entirely is submitted by T. N. Horan (Am. Rev. Tuberc. 32:166 (Aug.) 1935). A group of boys in a private school, in which not only the students but also the faculty, maids, workmen, etc., were examined carefully and x-ray pictures taken frequently, were studied in regard to the incidence of tuberculous infection. The percentage of positive Mantoux reactions in 3 successive school years was 47, 41 and 33 per cent., respectively. Thus, a definite progression toward a negative test was shown. It is stated that after about 2 years calcium is deposited in an appreciable degree in the tuberculous lymph nodes and healing progresses, in the absence of further contacts, with a fading of the tuberculin test from year to year until in some instances there may be a complete loss of the ability to react to tuberculin.

*Immunity.*—An attempt has been made by M. I. Levine (Am. J. Dis. Child. 51:1052 (May) 1936) to obtain further data on the question of the comparative immunity between the white and colored races. A study of the tissue reaction of 136 white, negro and Puerto Rican children inoculated intradermally with attenuated bovine tubercle bacilli (BCG) was made. The factors considered as criteria of tissue resistance were: (a) the evolution of the lesion; (b) the development of abscesses of the inguinal nodes draining the area of the local lesions; and (c) the rapidity of formation of inguinal abscesses.

The results are summarized as follows: The necrosis of the local lesion induced by inoculation with BCG occurred more rapidly in the tissue of negro children than in the tissue of white children. A higher percentage of negro and Puerto Rican children had inguinal abscesses following intradermal inoculation with BCG, and the inguinal abscesses formed more rapidly in negro



TABLE I  
Mortality from Tuberculosis in Children Vaccinated with BCG and in Unvaccinated Children

|                       | Exposed to Persons with Tuberculosis Whose Sputum Contained Tubercle Bacilli |                      |             | Exposed to Persons with Tuberculosis Whose Sputum Did Not Contain Tubercle Bacilli |                      |     | Not Exposed to Persons with Manifest Tuberculosis |                      |   |
|-----------------------|--|----------------------|-------------|--|----------------------|-----|---|----------------------|---|
|                       | Total No.  | Died of Tuberculosis |             | Total No.  | Died of Tuberculosis |     | Total No.   | Died of Tuberculosis |   |
|                       |  | No.                  | Per-centage |  | No.                  | %   |   | No.                  | % |
| Vaccinated. . . . .   | 41   | 1                    | 2.4         | 15   | 0                    | —   | 14*   | 0                    | — |
| Unvaccinated. . . . . | 84   | 10                   | 11.9        | 45   | 2                    | 4.4 | 38  | 0                    | — |

\* Diagnosis of manifest tuberculosis was not confirmed in 7 instances, while in the remaining 7 instances the mothers died of tuberculosis or remained in hospitals.

TABLE II  
Reactions to Tuberculin in Children Vaccinated with BCG and in Unvaccinated Children

|  | Number Tested | Positive Reactions to Old Tuberculin |    |          |    |       |    |
|--|---------------|--------------------------------------|----|----------|----|-------|----|
|  |               | To 0.01 Mg.                          |    | To 1 Mg. |    | Total |    |
|  |               | No.                                  | %  | No.      | %  | No.   | %  |
| Exposed to Persons with Tuberculosis whose Sputum contained Tubercle Bacilli       |               |                                      |    |          |    |       |    |
| Vaccinated.....  | 38            | 25                                   | 66 | 6        | 16 | 31    | 82 |
| Unvaccinated.....  | 79            | 49                                   | 62 | 14       | 18 | 63    | 80 |
| Exposed to Persons with Tuberculosis whose Sputum did not contain Tubercle Bacilli |               |                                      |    |          |    |       |    |
| Vaccinated.....  | 14            | 9                                    | 64 | 4        | 29 | 13    | 93 |
| Unvaccinated.....  | 44            | 7                                    | 16 | 9        | 21 | 16    | 36 |
| Not Exposed to Persons with Manifest Tuberculosis                                  |               |                                      |    |          |    |       |    |
| Vaccinated.....  | 8             | 3                                    | 38 | 3        | 38 | 6     | 75 |
| Unvaccinated.....  | 38            | 4                                    | 11 | 5        | 13 | 9     | 24 |

children than in white children. From this evidence the author concludes that, in general, the tissues of negro and Puerto Rican children seemed to be less resistant to inoculation with attenuated living bovine tubercle bacilli than are the tissues of white children.

**Prophylaxis.** — Evidence indicating that the administration of BCG vaccine to newborn infants exposed to patients with manifest tuberculosis may prove of value in reducing the mortality from this

disease in infancy and childhood is presented by J. D. Aronson and A. M. Dannenberg (*Ibid.* 50:1117 (Nov.) 1935). A group of newborn infants residing in families of known cases of manifest tuberculosis were vaccinated orally during the first 10 days of life with BCG. A group of infants similarly exposed but too old to be vaccinated by mouth at the time of their first examination were used as a control. The result of their experience is presented in tabular form in

TABLE III

*Age at which Pulmonary Lesions Recognizable by X-Ray Examination were Observed.*

| Age in Years | Exposed to Persons with Tuberculosis Whose Sputum Contained Tubercle Bacilli |                |                 |                  |                       |                |                 |                  |
|--------------|--|----------------|-----------------|------------------|-----------------------|----------------|-----------------|------------------|
|              | Vaccinated Children  |                |                 |                  | Unvaccinated Children |                |                 |                  |
|              | Infiltrations  | Enlarged Nodes | Calcified Nodes | Negative Results | Infiltrations         | Enlarged Nodes | Calcified Nodes | Negative Results |
| Under 1....  | 0  | 0              | 0               | 8                | 17                    | 8              | 0               | 6                |
| 1 to 2.....  | 4  | 0              | 1               | 4                | 8                     | 4              | 1               | 5                |
| 2 to 3.....  | 1  | 0              | 0               | 6                | 10                    | 2              | 10              | 6                |
| 3 to 4.....  | 1  | 0              | 2               | 6                | 6                     | 3              | 7               | 8                |
| 4 to 5.....  | 0  | 0              | 1               | 3                | 1                     | 2              | 4               | 5                |
| 5 to 6.....  | 0  | 0              | 1               | 2                | 1                     | 0              | 1               | 7                |
| 6 to 7.....  | 0  | 0              | 0               | 1                | 0                     | 0              | 2               | 0                |
|              | 6  | 0              | 5               | 30               | 43                    | 19             | 25              | 37               |

TABLES I, II and III, taken from their article.

Experiments on the immunization of guinea-pigs with heat-killed and formol-killed tubercle bacilli administered by different routes have been carried out by A. Branch and J. F. Enders (*Am. Rev. Tuberc.* 32: 595 (Nov.) 1935). Their results are in accord with earlier observations and show that young cultures of virulent tubercle bacilli, killed by heat, give satisfactory results as a prophylactic vaccine in guinea-pigs. In these experiments the organisms were killed at 65° C. and not at 100° C. Intramuscular route of administration of the vaccine was found to be more efficacious than the intravenous or intraperitoneal routes. Organisms killed by formalin were no more effective than were heat-killed bacilli. The authors suggest that experiments be continued to assay the protective value of vaccine of dead tubercle bacilli, killed by other methods than those used in these experiments, in the hope of finding a still more efficacious dead vaccine. This is important in view of the controversy regarding the safety in the use of avirulent living tubercle bacilli as a vaccine. The authors found no correlation between the degree of skin-test reactivity of individual animals to

tuberculin following vaccination and before infection and their period of survival after infection (immunity).

An attempt to "desensitize" tuberculous guinea-pigs with dead vaccine and products of the tubercle bacillus has been made by C. L. Derick, E. A. G. Branch and M. P. Crane (*Ibid.* 32: 218 (Aug.) 1935). This work was stimulated by that of Swift and his co-workers on rheumatic fever. They were able to produce in rabbits a hypersensitive condition to streptococci. This state of hypersensitiveness resembled in many respects that found in tuberculosis. These workers were also able to change the animals from this hypersensitive state to one of immunity or hyposensitiveness by appropriate treatments with living and killed streptococcus vaccines. Derick and his coworkers found that subcutaneous vaccination of tuberculous guinea-pigs with killed tubercle bacilli resulted in quantitative diminution of the intracutaneous tuberculin reaction and a prolongation of life over control animals. No substantial results were obtained with formol-killed bacilli, Koch's bacillary emulsion, or the acetic-acid precipitable protein fraction. Whether any satisfactory antigen for active desensitization can be found remains to be determined and whether or

not active desensitization in the human being will be attended by an increase in immunity is not proved. This seems to be a field worthy of further investigation.

**Treatment.**—The use of the *tuberculin test as a guide in terminating artificial pneumothorax* is suggested by J. R. Neal (*Ibid.* 32:326 (Sept.) 1935). Assuming that persons with a negative tuberculin test were not tuberculous, the author believes that the failure to obtain a skin reaction to tuberculin may be used as a criterion for terminating artificial pneumothorax in patients being treated for active tuberculosis. Tuberculin was given in an amount up to 10 mg. intracutaneously before patients were considered to be nonreactors. Seven out of 8 patients treated in this manner were negative to 10 mg. of tuberculin after 6 months' time and clinically had no evidence of tuberculous disease. The author agrees that 6 months is too short a period of observation and that his series of cases is too small for definite conclusions, but he believes that this study opens up a new field for further investigation.

The effect of **irradiated milk** on experimental inhalation tuberculosis in guinea-pigs has been observed by D. F. Loewen and W. H. Oatway, Jr. (*Ibid.* 33:733 (June) 1936). Irradiated cream was added to the diet of groups of nor-

mal and sensitized guinea-pigs who were subsequently infected by the spray inhalation method. Their observations disclosed no remarkable prophylactic or therapeutic effects, as judged by the extent or type of the resultant lesions or by the mortality statistics, when the pathology of the groups receiving the irradiated cream was compared with that of the control group. Suggestions of a favorable effect were noted in the group receiving irradiated cream, but they were not considered great enough to be of significance. It was suggested that the effect might be of different importance when translated to human infection. The groups receiving irradiated cream exhibited a sustained, higher average weight curve than the control groups. Calcium deposits were found during gross and microscopic examination only in the tissues (and lesions) of tuberculous animals. The calcium content of the lungs of the infected animals was found to be greater than that of the uninfected, and was in quantitative relationship to the amount of disease present in the lungs. The occurrence of calcification and of abnormal calcium content of the lungs was found to be independent of the vitamin or calcium intake of the animals. No untoward effects were observed in those animals fed irradiated cream.

## WHOOPING COUGH

By ROBERT A. LYON, A.B., A.M., M.D.

**Diagnosis.**—Severe sneezing was the most common symptom of whooping cough in 2 children observed by A. C. Rambar (*J. Pediat.* 8:582 (May) 1936). One of these patients was 23 months of age and the other 18 months of age. In each case the attacks of *paroxysmal sneezing* occurred for 3 weeks before the typical whooping and coughing of per-

tussis developed. In one child, the leukocyte and differential counts led to the diagnosis of whooping cough and, in the second instance, the disease was suspected because the patient's sister had typical symptoms of whooping cough.

The significance of the number and types of *leukocytes* in the diagnosis of whooping cough has been investigated

recently by N. D. Begg and M. F. Coveney (Lancet 2:1113 (Nov. 16) 1935). They studied the blood of 65 patients, 3 months to 9 years of age, who were in the late catarrhal or early paroxysmal stage of the disease. Comparisons were made with the average counts and differential analyses of normal children of the same ages. Of interest was the fact that the lymphocytes in 23 per cent. of the pertussis group were not increased in number above normal figures and in the infants less than 6 months of age only 33 per cent. had an increase in the total number of lymphocytes. It was found that the leukocyte count usually returned to normal within a period of 2 weeks after the beginning of the whooping stage. Although the authors felt that the blood analysis was an important aid in the diagnosis of pertussis, nevertheless they stressed the point that there were numerous deviations from the typical picture, especially in younger children.

**Complications.**—The *central nervous system* is frequently involved during attacks of whooping cough. Symptoms of intracranial damage have been observed in 10 to 20 per cent. of patients with pertussis, especially in infants and younger children. W. Bayer (Klin. Wchnschr. 14:1032 (July 20) 1935) believed that it was important to examine the cerebrospinal fluids of uncomplicated cases of whooping cough to see if changes occurred there without any neurologic symptoms. Of 102 such patients, 50 were found to have some pathologic changes of the cerebrospinal fluid without any clinical evidence of involvement of the central nervous system. Abnormal findings in the cerebrospinal fluids included increases in amount and in pressure, elevated cell counts, increased amounts of globulin, variations in the mastic curves like those found in cases of meningitis, and a lowering of the bar-

rier between the blood and cerebrospinal fluid as measured by injections of a dye (uranin). These changes occurred singly or in combination with each other. Some of these patients who were without nervous symptoms had as many abnormalities of their cerebrospinal fluids as patients with convulsions or other nervous symptoms with whooping cough. It was thought that the brain was affected by toxic substances of the infection, together with edema arising from the mechanical influence of the paroxysms.

An unusual complication of whooping cough reported by W. Edgecombe (Lancet 2:374 (Aug. 17) 1935) was the *fracture of 2 ribs* during paroxysms of the disease. The patient was a young adult, 18 years of age, who cracked the eleventh rib on one side during a coughing spell and subsequently fractured the eleventh rib on the other side during another paroxysmal attack. There was no evidence of any bone disease or calcium deficiency in this patient, although she had fractured 2 bones on previous occasions in her life.

**Treatment.**—**Convalescent serum** has been found to be of some value in the treatment of children exposed to whooping cough. D. Paterson, R. H. Bailey and R. G. Waller (*Ibid.* 2:361 (Aug. 17) 1935) employed this therapy in a group of 25 to 30 patients who had already developed the symptoms of whooping cough, but it seemed to have very little effect in this stage of the disease. In a series of 95 patients between 1 month and 4 years of age who had been exposed to the disease, the administration of convalescent serum seemed to produce mild attacks or totally prevented the disease in a much larger percentage of patients than in an untreated control group of children of approximately the same age distribution.

Both **convalescent serum** and **immune adult blood** were thought by

W. L. Bradford (Am. J. Dis. Child. 50:918 (Oct.) 1935) to be of some value in the early treatment and prevention of whooping cough. Convalescent serum collected during the eighth week of convalescence from whooping cough was given to 12 children, the majority of whom were under the age of 3 years, and whole blood from immune adults was given to 15 other children who were exposed to whooping cough in their homes. The incidence, severity and number of complications were greatly reduced in this group of children as compared with an untreated control group. Another group of 17 children were given one or the other of these materials during the first stages of their catarrhal period, but there was no difference in the course of the disease as compared with that of a control group. In a third group of 16 children who were exposed outside of their homes, the materials seemed to give entire protection against the disease. It was the conclusion of the author that the immune blood contained antibodies against whooping cough which, when given early in the incubation period of the disease, was effective in modifying or preventing the symptoms.

**Pertussis vaccine** prepared by modern methods was used without success in the treatment of patients with active whooping cough by N. D. Begg and M. F. Coveney (Lancet 1:82 (Jan. 11) 1936). Every other patient of a group of 60 children with pertussis was given pertussis vaccine in doses of 0.2, 0.5, 1.0, 1.5, 2.0 and 2.5 c.c. at 2- or 3-day intervals. The course of the disease was approximately the same in each group except that more of the treated children continued to whoop after the fourteenth day than those of the untreated group. Occasionally, a fever reaction of short duration followed the injection of the vaccine.

**Gold tribromide** has been advocated for several years by J. Epstein (Arch. Pediat. 53:52 (Jan.) 1936) for the treatment of pertussis. The author has now observed the effects of its use in 300 patients. It was administered in the form of the elixir in doses of a teaspoonful every 3 hours until relief was obtained, and then the intervals between doses were gradually lengthened as the progress of the disease indicated. The gold tribromide has also been added to water and employed as a *steam inhalation* with relief of symptoms. In the comparison of the course of whooping cough of children treated with some form of gold tribromide and those treated with other methods, it appeared to the author that the course and severity of the illness was reduced by this specific therapy.

A comparison of the therapeutic results of **pertussis vaccine** and **gold tribromide** in a group of 26 infants under 2 years of age was made by H. C. Thompson, Jr. (*Ibid.* 52:569 (Aug.) 1935). One-half of the group was given 3 injections of the vaccine which was prepared by the New York State Department of Health, 8 of the remaining number of children received gold tribromide, and the other 5 received no treatment. A comparison between the three groups was made in regard to the severity and the duration of the attacks, the patients' loss of weight and other complications. The children who received the vaccine at the onset of symptoms did not seem to be benefited in any way, while the 8 infants who received elixir of gold tribromide during the spasmodic stage of the disease lost less weight and seemed to have less severe paroxysms than the other children.

**Prevention.**—In a recent review of the success of **whooping cough vaccine**, L. Sauer (New England J. Med. 213:1061 (Nov. 28) 1935) mentioned the fact that of a group of 394 children

who had received the vaccine in a course of seven years, 27 had been intimately exposed to pertussis of their brothers or sisters. Twenty-six of these children escaped the infection and 1 developed a mild attack. Larger groups of children treated with the commercial preparations of this vaccine have been observed for shorter periods of time and the results have been satisfactory so far. The failure of the vaccine to be effective in affording protection was thought to be due to (1) its administration during other illnesses of the child which seemed to prevent the formation of sufficient antibodies; (2) the inactivation of the vaccine by alcohol sometimes used for sterilizing the syringes; (3) the deterioration of the vaccine when not stored at cold temperatures; and (4) the possibility that the dosage of 8 c.c. is not sufficient for older and heavier children. The best age for vaccinating against whooping cough was thought to be 7 to 12 months.

In order to determine the *susceptibility* of the patient to whooping cough, Paterson and Waller (*loc. cit.*) used intradermal injections of the vaccine. They found that many patients who had had the disease previously gave positive reactions characterized by an area of erythema which developed at the site of the injection in 24 to 48 hours after the test. Those who were susceptible to the disease usually had no reaction to the intradermal test. The skin test was ap-

plied to a group of children who were vaccinated with the **Sauer whooping cough vaccine**, which was administered in 6 successive doses at intervals of 3 or 4 days. Within a week after the last injection, children who had previously had negative skin tests developed positive ones, and it was thought that the immunity received from the vaccine treatment developed in a much shorter time than the 6 months suggested by Sauer.

**Pertussis vaccine**, somewhat similar to that of Sauer, has been prepared by P. Kendrick and G. Eldering (*Am. J. Pub. Health* 26:8 (Jan.) 1936). *Pertussis bacilli* (phase I) were grown on Bordet-Gengou medium enriched with 15 per cent. sheep's blood instead of human blood as recommended by Sauer. The organisms are killed by the addition of merthiolate, 1:10,000, or phenol, 0.5 per cent., which is allowed to act for a week or more at cold-room temperature. Amounts of 6.0 to 7.5 c.c. have been employed, usually in 4 divided doses. A total of 712 children have received this vaccine and the incidence of pertussis in this group has been compared to that of a control untreated group of 880 children of about the same age. Up to the present time, 67 cases of whooping cough have developed and only 4 of these were among the vaccinated group. These 4 children had mild symptoms, while only 10 of the 63 cases in the control group had light attacks, the remainder being moderate or severe.

# NEUROLOGY

Edited by BERNARD J. ALPERS, M.D., D.Sc.

## BRAIN TUMORS

By R. A. GROFF, M.D.

**PITUITARY TUMORS AND PARASELLAR LESIONS.—Classification.**—The terminology applied to the component parts of the hypophysis, *i. e.*, the pars anterior, the pars intermedia, and the pars posterior, have been generally accepted. Primary pituitary tumors arise from the pars anterior and take their name from the cells of the gland from which they arise. C. H. Frazier and B. J. Alpers have aided greatly in clarifying the terminology of parahypophyseal lesions, which are commonly called *tumors of Rathke's pouch* and *craniopharyngeal tumors* or *craniopharyngiomas*. These last two terms, according to the writers and Tilney, are unquestionably misnomers and misleading. In its origin, a tumor of Rathke's pouch has no relation to the pharynx. The so-called craniopharyngioma, on the contrary, takes its origin from an anlage of the original stalk from the buccal cavity. As a substitute for craniopharyngioma, they suggest the term *tumor of the hypophyseal stalk*. They further suggest that the term tumor of Rathke's pouch should give way to tumor of Rathke's cleft. In the terms of the anatomist, Rathke's pouch is an invagination from the roof of the primitive oral cavity. In the process of development it becomes constricted and a sac with a narrow stalk is formed. The sac eventually closes and the stalk, originally connected with the mouth, usually disappears. This

stalk persists, in some cases, as does the thyroglossal duct, and it is from these epithelial rests that tumors of the stalk have their origin. The original Rathke's pouch becomes converted into a solid structure, the pars anterior, or the glandular lobe of the hypophysis. A small cleft remains between the pars anterior and the pars posterior or processus infundibuli. This is all that remains of the original pouch as described by Rathke, and it is from this cleft that the tumors under discussion originate. From these anatomical considerations the authors feel that Rathke's pouch tumors should be designated as *tumors of Rathke's cleft*.

Frazier and Alpers present a case in which, by the presence of a single layer of ciliated columnar epithelium, they made a diagnosis of tumor of Rathke's cleft. They cite the studies of Duffy, who found that the hypophyseal vesicle or sac, a later stage of Rathke's pouch, is composed of stratified cylindrical epithelium; most of this tissue develops into the anterior lobe, but a single layer of cylindrical epithelium persists in the adult gland as the "cleft." On the other hand, the hypophyseal duct is composed of modified squamous epithelium, which gradually passes over into the cubical epithelium of the buccal canal.

From the study of human hypophyses, in some instances ciliated cells have been found lining the remains of Rathke's cleft and they conform in their morph-

ology to the types of cell seen in the case presented. From a theoretical point of view, tumors of Rathke's cleft should be found within the sella turcica, but when consideration is given to the origin of the anterior lobe from the buccal epithelium and the process of traversal and rotation during the course of its development, it is not surprising to find such tumors wholly outside the sella turcica.

In *differentiating* these tumors from lesions in the immediate neighborhood, such as tumors arising from the ependyma, the authors state that the presence of columnar rather than cuboidal cells would indicate a Rathke's cleft lesion. Colloid tumors of the third ventricle are similar in all respects to the tumor described, but it is their feeling that it is difficult to connect them with cysts of Rathke's cleft. Furthermore, the wall lining of such a cyst is similar to that of the cyst of Rathke's cleft, but otherwise the tumors are dissimilar. From these anatomical, embryological, and histological studies it is apparent that the nomenclature of Rathke's cleft should be substituted for tumors of Rathke's pouch, and hypophyseal stalk tumors for craniopharyngiomas. It seems that this work is the first attempt to clarify an already too vague terminology for congenital tumors of the pituitary gland.

**Pituitary Adenoma.**—TREATMENT. —during the period of 1926 to 1927, the patients in the clinic of Harvey Cushing having pituitary adenomas were operated upon by the transphenoidal route. Since that time, the **transfrontal approach** advocated by Frazier has completely replaced the transphenoidal operation. The only information that can be gathered from a study of these patients is that the transphenoidal operation does not accomplish with any degree of certainty the results obtained by the transfrontal approach to the pituitary. (H. Cairns: *Lancet* 1: 1223 (May 30) 1936.)

### ***Basophilic Pituitary Adenoma.\****—

Since the description by Cushing of the syndrome consisting of obesity, hirsutism and menstrual disorders, and in some instances associated with hypertension, *striae distensæ abdominis*, osteoporosis, exophthalmos, and glycosuria associated with a basophilic adenoma, there have appeared in the literature many similar case reports. At the same time, considerable discussion has occurred as to the validity of connecting the syndrome with the proliferation of basophilic cells in the pituitary gland.

W. Susman (*Brit. J. Surg.* 22: 539 (Jan.) 1935) reported upon a series of 260 pituitary glands removed at autopsy, irrespective of the presenting disease. Of this group, 22 contained 23 tumors and of these, 20 were of a purely incidental character and had given rise to no symptoms. Of these incidental tumors, 4 were acidophilic, 8 basophilic, and 5 chromophobe. The lesions varied from 0.2 mm. in diameter to 7 by 3.5 mm. These tumors occurred in no specific age, sex or disease group. From his studies, Susman showed that of the whole series of 260 cases, 21 cases presented pituitary glands in which there was a definitely high basophilic cell content. No specific cause was determined. The conclusions drawn are that the abundance of basophilic cells in the anterior lobe of the pituitary is not peculiar to any age, sex, or disease group. If these cells produce a hormone important to the sex mechanism of the individual, a definite difference could be expected, both with justification and without exception, as between infants and children, as sexually immature and practically sexless on the one hand, and the adults on the other. This, however, was not the case. The incidence of cases showing a high basophilic cell content in the anterior pituitary was high

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See also section on ENDOCRINOLOGY.



between the ages of 40 and 60 years, but almost 40 per cent. of all the cases in the whole series belonged to this age period.

The author's conclusion is that the histological data from this series of 260 hypophyses give no support to the contention either of Zondek, that the basophilic cells of the anterior pituitary secrete a sex hormone, or of Cushing, that hypersecretion of basophilic cells caused by the presence in the anterior pituitary of the basophilic adenoma and of the area of basophilic hyperplasia will give rise to a syndrome which he has termed "pituitary basophilism." Adenomas as a whole occur in 8 per cent. of cases, the basophilic type in 3 per cent., and thus they are too common to be of any special significance.

M. A. Goldzieher and H. Koster (Am. J. Surg. 27:93 (Jan.) 1935) have contrasted the basophilic syndrome with that of adrenal cortical hyperfunction. They cite numerous examples from the literature in which the evidence of basophilic hyperplasia of the pituitary is not the entire factor in the production of the basophilic syndrome. Reichman reported a case with comparable symptoms showing eosinophilic adenoma of the pituitary gland. Moehlig recently reported the occurrence of a primary malignant tumor of the adrenal cortex which showed extensive hyperplasia of the basophilic cells of the pituitary and symptoms of Cushing's basophilism. The authors report 5 cases in which there were present the tripartite symptom complex of obesity, hirsutism and menstrual disorder. In each of these 5 cases the adrenal glands were exposed and either a bilateral partial section of the gland was performed or one gland removed. Pathological studies of the glandular tissue showed the formation of the unusually broad reticular layer of the cortex. This layer stands out not only by its abnormal

width, but also by the intense staining of cell bodies with eosin.

The authors point out that *hirsutism* of pituitary origin is usually silky, lanugo-like, and facial growth predominates on the cheeks. The hirsutism caused by abnormal ovarian function is universal and of typical masculine character. That due to adrenal cortical hyperactivity is characterized by coarse, dark hair on the chin and upper lip beside wide distribution all over the body.

An attempt to distinguish the *obesity* caused by one glandular disturbance from all others is difficult. Nevertheless, the "girdle" characteristics of the *pituitary type*, the generalized adiposity of the *ovarian type* with its trochanteric pad, and the torso distribution of the *adrenal cortical type* are suggestive of these different etiological factors.

The result of a survey of ovarian, pituitary and adrenal pathology in relation to *menstrual disturbances* shows that abnormalities of menstruation are associated with various changes in either of these three glands. The type of menstrual disorder is in no way pathognomonic for any particular endocrinopathy, except perhaps for menorrhagia, which is more likely to be associated with primary ovarian change or disturbances secondary to pituitary disease.

**GLIOMAS.—Diagnosis.**—The investigation of the sense of smell and its use in the diagnosis of brain tumors has been ingeniously utilized by C. A. Elsberg (Bull. Neurol. Inst. New York 4:535 (Apr.) 1936). In a series of 47 tumors in or under the *frontal lobes*, the localization was made by the olfactory tests in 46 instances. In 25 cases of *extracerebral tumors* which lay under one or both frontal lobes, the minimum identifiable odor (M. I. O.), which is the standard used by Elsberg, was elevated on one or both sides, while the duration of fatigue was not prolonged beyond

normal. In 11 cases of *intracerebral tumor*, the M. I. O. was elevated on the side of the tumor and the duration of fatigue was prolonged on the same side. "In a patient with an *intracranial tumor* in whom the M. I. O. is elevated but the duration of fatigue is not prolonged, the growth is situated underneath the corresponding frontal lobe; if there is unilateral elevation of M. I. O. and prolongation of olfactory fatigue on the same side, the tumor is in the substance of the corresponding frontal lobe."

**Prognosis.**—Since the publication of an article by van Wagenen upon the life expectancy of patients with various types of intracranial neoplasm, H. Cairns (Lancet 1:1223 (May 30) and 1291 (June 6) 1936) reported the results of 148 cases operated upon in the clinic of Harvey Cushing between the years 1926 and 1927. These statistics are extremely valuable and provide good insight into the prognosis of the most frequent types of intracranial lesions. Of the 148 cases in which tumors were partly or wholly removed at operation, 135 survived. Contact was maintained with all of the survivors between the years 1927 and 1935.

Considering the entire group of patients, the author's statistics show that 37 among the 157 operated upon were useful survivors. This gives a useful survival rate of 23.5 per cent.; or if only the 135 patients who survived the dangers of operation are considered, a useful survival rate of 27.4 per cent. Thus, for patients with verified intracranial tumors undergoing operative treatment, the chances of useful survival for a period of 7 to 9 years were roughly 1 in 4.

Of the whole series of 157 cases, 14 per cent. died within a few weeks of operation; a further 12.7 per cent. after leaving the hospital died in the first year; 12.1 per cent. died in the second year; while in the third year the percentage dropped to 5.1 per cent., and

remained thereafter low. At the end of 7 to 9 years, 40 per cent. were alive and 23.5 per cent. were living a useful life. It is true, as the author points out, that the incidence of benign tumor in this series is greater than would be found in a series of unselected tumors, but the statistics upon the individual types of intracranial lesions give an insight into prognosis of each type of brain tumor. With this information a better knowledge of the problem is afforded.

In his consideration of the glioma group, Cairns collects the following data for the more common types of glioma:

*Glioblastoma Multiforme.*—This tumor grows very rapidly, as shown by a very short history and evidences of extreme malignancy in pathological study. It is usually found in middle-aged and elderly individuals. It is infiltrating, not affected materially by x-ray, and recurrence in most cases is rapid. In this series there were 8 cases. In 6 cases removal of the tumor at operation appeared to be complete, and in the other 2 partial. The shortest survival period from the time of operation was 2½ months, the longest 14 months, the average about 6½ months.

*Cerebellar Medulloblastoma.*—This is a tumor confined almost entirely to children and young adults, arises usually in the vermis and at operation appears to be fairly well defined. It recurs rapidly, disseminates by metastases, and is favorably influenced by **x-ray** and **radium**. In this series there were 5 cases. All died at intervals of 2 to 19 months after operation. The average survival period was 13 months. It is interesting to note that though the survival period is short, the proportion of useful life in this short survival is usually high.

*Cerebellar Astrocytoma.*—This proves to be one of the most satisfactory intracranial tumors to deal with surgically. It occurs chiefly in young adults and

children, in the vermis and lateral lobes of the cerebellum, and appears to be almost invariably quite circumscribed and benign. If all the tumor tissue visible to the naked eye is removed at operation, the tumor does not, as a rule, recur. In this series there were 4 young female patients with this type of lesion. Three of these patients were well, in full work, and free from symptoms over a period of 7 to 9 years after operation. The fourth patient died 14 months after a second attempt was made to remove a partially extirpated lesion.

*Cerebral Astrocytoma.*—This type of tumor differs from the cerebellar astrocytoma in being less sharply defined and not wholly composed of astrocytes. There is also evidence of malignancy. These tumors are difficult to remove completely and recurrence after apparently complete removal of the tumor is common. There were 15 cerebral astrocytomas and all but 4 died within 3 years; 8 of the 15 patients had a second operation for recurrence of tumor. The average survival period for the whole group was 37 months.

**Treatment.** — EFFECTS OF X-RAY UPON GLIOMAS.—At the meeting of the Association for Research in Nervous and Mental Diseases, December 27, 1935, a report was made by C. H. Frazier and B. J. Alpers on the effects of irradiation on the gliomas. This study was based upon all available material from the various large neurosurgical clinics in the United States. Certain definite criteria were used in the selection of cases. Thus, the study consisted entirely of pathological material of cases with glioma and, with but one or two exceptions, only those cases were used in which there was a pre- and postradiation specimen. Adequate treatment was considered when the tumor dosage ranged from 2000 r upward. Moderate treatment consisted of a tumor dose from 1000-2000 r and in-

adequate treatment was considered when the tumor received less than 1000 r.

The following table gives the types of tumors studied and the number in each group:

|                                   |       |
|-----------------------------------|-------|
| Medulloblastomas . . . . .        | 32    |
| Glioblastoma multiforme . . . . . | 55    |
| Astrocytoma . . . . .             | 39    |
| Oligodendroglioma . . . . .       | 15    |
| Ependymoma . . . . .              | 10    |
| Craniolioneuroma . . . . .        | 2     |
| Astroblastoma . . . . .           | 3     |
|                                   | <hr/> |
|                                   | 156   |

The effects of irradiation are considered under the respective groups.

*Medulloblastoma.*—There were 24 tumors of the type analyzed. Of these, 19 showed definite effects of irradiation and 4 were without any visible histological effect. Of the 19 which were definitely affected, 11 exhibited mild changes, and 4 moderate changes in the structure of the tumor. The changes which occur in these tumors are primarily on the cells and blood vessels. Where examination permitted the study of the peripheral and deeper portion, it was found that the histological changes were invariably more pronounced in the peripheral portions of the tumors. These results show conclusively that the medulloblastoma group is radiosensitive.

The authors conclude that the cells in individual tumors show wide variations in radiosensitivity and regenerative ability and that the medulloblastomas as a group showed marked difference in their response to irradiation. They feel that from the comparison of histological changes and the amount of x-ray treatment, the irradiation therapy should be planned to destroy the most radioresistant cells and to inhibit cell regeneration. This can be obtained by using the maximum number of skin portals and treating each one to the limit of skin tolerance.

*Glioblastoma Multiforme.*—Forty-one tumors of this group were studied. Of

these, 9 showed marked response to irradiation, 9 a mild response, and 21 no response at all.

The effect upon the tumor after irradiation was variable. The changes noted were mild or moderate necrosis, a decrease in the cell count, a reduction in the number of giant cells, and occasionally fewer mitoses. The blood vessels and connective tissue may be definitely affected. The authors state that too much reliance cannot be placed on these findings, because changes of the type described are so frequently seen in the glioblastoma multiforme group as a part of their natural growth.

The histological changes paralleled roughly the intensity with which the tumor was irradiated. The conclusion reached was that intensive irradiation with shorter intervals between irradiation is indicated.

*Astrocytomas.*—Of this type, 33 tumors were analyzed. Six showed marked responses to irradiation; 5 showed moderate response; in 20 the response was mild; and in 2 there was no response at all.

Irradiation effects, when present, in the astrocytomas were seen chiefly in the cellular structures, and to a much milder degree in the blood vessels and connective tissue. Necrosis is much more marked following irradiation of these tumors and is more significant in this type of tumor as compared with the glioblastoma group, since it is unusual to find the astrocytomas becoming necrotic during their period of growth. These tumors must be regarded as showing a sufficient response to irradiation to justify this treatment wherever it is indicated.

*Ependymoma.*—Of the 7 cases studied, 2 showed marked changes, 1 definite changes, 3 mild changes, and only 1 showed no response at all.

The histological changes demonstrated were a definite tendency of the cells to

mature, an increase in the multinucleated forms, and a decrease in the number of cells by actual count. The connective tissue is sometimes increased to a marked degree. These changes show conclusively that ependymomas are radiosensitive.

The analysis in this group from a tumor dosage standpoint would indicate a certain degree of radiosensitivity which is roughly proportional to the amount of irradiation delivered to the tumor.

*Oligodendrogliomas.*—There were no significant changes demonstrated in this tumor group which could be attributed to irradiation.

With the evidence presented, it is clear that the medulloblastomas are most sensitive of all glioma to irradiation, but a definite response is shown also by the ependymomas and astrocytomas. A mild response is exhibited by the glioblastoma multiforme group, and no response is shown by the oligodendrogliomas.

**MENINGEAL FIBROBLASTOMAS.**—These tumors are the most favorable from the standpoint of complete removal without recurrence of all intracranial lesions. They are well encapsulated, often extremely vascular and for this reason difficult to remove. Of the 31 patients reported, 5 died after operation. Of the 26 survivors, 8 have since died at varying intervals, all from recurrence of the tumor. In 6 of these cases the tumor was known to have been only partly removed at operation, but in the other 2 removal of the tumor had apparently been complete. Thus, 18 patients were alive and well 7 to 9 years after operation; 44 per cent. of the survivors were completely well and at work; 33 per cent. were at work, but had major symptoms; the remaining 23 per cent. were living but unable to work. It must be remembered, as the author states, that the technic of treatment has improved since 1926 and that results obtained today would be much more encouraging.

**ACOUSTIC FIBROBLASTOMA.**

Ten tumors of this type were operated on by the method of **intracapsular extirpation**. Two patients died, 1 in the hospital and another 3 years after operation from bronchiectasis. Eight patients were still living 7 to 9 years after operation. Two were in full work. Three were unable to work and were completely or severely incapacitated by ataxia. The remaining 3 had done light work.

These statistics offer a means of evaluating the surgical treatment of brain tumors. The advance in the technic of neurosurgical procedures has been tremendous and for this reason the results obtained in the meningeal fibroblastomas and acoustic neurofibroblastomas would certainly be better. However, the statistics concerning the gliomas would not materially be changed, except where x-ray treatment has been found to be a definite aid in inhibiting their growth.

**COLLOID CYSTS OF THIRD VENTRICLE.**—A. J. McLean (Arch. Neurol. and Psychiat. 36:485 (Sept.) 1936) sheds new light upon the origin of these tumors. He shows that the vestigial structures arising from the midline roof of the third cerebral ventricle arise from the paraphysis. The function of this structure is unknown. As these cysts enlarge, they project downward through the velum, to hang pendulous within the lumen of the third ventricle.

The content of the cyst is usually unorganized, turbid, milky, tenacious colloid material, with generous flecks or streaky blobs of yellowish brown, soft, diffuent

pigment. Cholesterol crystals have been observed microscopically in the fluid. The colloid itself is noncharacteristic and may contain swollen cells, erythrocytes, leukocytes, gutter cells and desquamated epithelium.

**Clinical Aspects.**—McLean quotes statistics from Stookey in which 45 per cent. of the reported cases of cystic tumors of the third ventricle presented the complete cardinal triad of symptoms indicating intracranial tension (headache, vomiting, choked disc) and that in 90 per cent. at least one of the components was present. In 39 per cent. striking instantaneous relief of headache had been obtained by special postures of the head, probably as a result of the slight gravitational shift of the pendulous tumor away from the foramina of Monro. This sign is very important in indicating a possible third ventricle tumor, since most of these cysts produce a ball-valve effect by blockage of the third ventricle and foramina of Monro. In 60 to 85 per cent. there were signs of diencephalic localization (diplopia, ptosis, anisocoria). In from 36 to 68 per cent. peculiar convulsive-like attacks with loss of consciousness were noted, while paroxysmal or progressive hemiparesis or hemianesthesia was observed in from one-third to one-half of the cases.

Ventriculography usually establishes the diagnosis, but the occurrence of headache and its relief with change of posture of the head is extremely helpful in making a clinical diagnosis even in the absence of signs of increased pressure.

**SPONTANEOUS INTRACRANIAL HEMORRHAGE**

By R. A. GROFF, M.D.

W. M. Craig and A. W. Adson (Arch. Neurol. and Psychiat. 35:701 (Apr.) 1936) have recently summarized the literature concerning the etiology of this problem and have stressed the surgical

treatment for it with a report of 9 cases in which a **craniotomy** was performed.

According to the authors, Cushing was probably one of the earliest surgeons actually to carry out surgical treatment for

the condition. Russell and Sargent reported 1 case with recovery, Penfield 2 cases, and Naffziger and Jones 2 cases of delayed traumatic intracerebral hemorrhage.

Of the 9 cases observed by Craig and Adson, 3 were the result of trauma, 1 following emotional strain, 1 rheumatic heart disease and endocarditis, and the cause of 4 was unknown. All these cases were operated upon by means of an osteoplastic flap and in each the convalescence was uneventful, except in 1 case, where the patient collapsed and died on the ninth postoperative day. The authors

assume that the cause of death was probably from a large hemorrhage from an aneurism of the circle of Willis. The recovery of the patients was in most instances complete. However, where the hemorrhage involved vital structures, residual symptoms occurred.

The *diagnosis* of spontaneous intracerebral hemorrhage may be confused with brain tumor with the one exception in which there is a preceding history of trauma. The symptoms are not characteristic, but the rapidity of the history and neurological signs may be very suggestive.

## CEREBRAL CIRCULATION

By ELI MARCOVITZ, M.D.

**Physiology.**—C. F. Schmidt (Amer. J. Physiol. 114: 572 (Feb.) 1936) studied the circulation in the parietal cortex of anesthetized curarized cats by a thermoelectric method. He found that on stimulating the cervical sympathetic vasoconstriction occurred in the parietal cortex. This response was slow in onset, development, and recovery. Section of the cervical sympathetic regularly caused vasodilatation in the parietal region. No vasodilator innervation could be detected by stimulation of the vagodepressor and carotid sinus nerves.

Changes in CO<sub>2</sub> and oxygen content of the blood were found to affect the blood-flow in the parietal cortex in the same manner as had previously been found to occur in the medulla and hypothalamus. "Increased CO<sub>2</sub> and decreased oxygen caused vasodilatation, decreased CO<sub>2</sub> and increased oxygen caused vasoconstriction. The effects of oxygen were more intense in the parietal region than in the other areas."

"Adrenalin had no vasoconstrictor effect in the parietal region; pituitrin, histamine, acetyl choline, and nitro-

glycerin were vasodilator. In the hypothalamus adrenalin was weakly vasoconstrictor and pituitrin had no apparent effect." The author stressed that "the vasodilator effect of CO<sub>2</sub> is the most potent single influence upon all parts of the cerebral circulation, and that an intrinsic regulation through this agency is probably the chief factor in the normal regulation of the cerebral circulation as a whole.

F. A. Gibbs, E. L. Gibbs and W. G. Lennox (Am. Heart J. 10: 916 (Oct.) 1935), by means of a thermoelectric blood flow recorder, introduced into the internal jugular vein of unanesthetized human subjects, investigated changes in cerebral blood flow after injections of adrenalin chloride, caffeine sodium benzoate, and histamine, and amyl nitrite inhalation. They found that intravenous injection of amounts of adrenalin chloride sufficient to cause a marked rise in blood-pressure, caused a great increase in cerebral blood flow, this increase undoubtedly being secondary to increase in blood-pressure. Minute amounts of adrenalin caused a slight rise in flow

without change (or with a fall) in blood-pressure, suggesting a vasodilator action.

"Intravenous injection of caffeine sodium benzoate usually caused a decrease in flow, with eventual restoration to a normal or slightly more than normal level. Since this occurred in the face of an invariable rise in blood-pressure, a temporary constricting action, perhaps secondary to respiratory stimulation, is indicated.

"Inhalation of amyl nitrite produced usually an increase in flow in spite of a decrease in blood-pressure, indicating a pronounced dilatation of cerebral vessels.

"Intravenous injection of histamine in one case caused a gradual but progressive increase in blood flow, independent of blood-pressure changes."

W. G. Lennox, F. A. Gibbs and E. L. Gibbs (Arch. Neurol. and Psychiat. 34:1001 (Nov.) 1935) studied the cerebral blood flow and the oxygen saturation of the blood returning from the brain in 22 unanesthetized human subjects, with reference to the loss of consciousness associated with (1) syncope (spontaneous or induced, (2) the breathing of nitrogen, and (3) a hyperactive carotid sinus reflex. They found that the subjects tested could be divided into 2 groups: "First are those in whom unconsciousness was preceded by a sharp fall in the volume of cerebral blood flow or was accompanied by a very low oxygen tension in the blood leaving the brain. In these cases the patient was always unconscious if the oxygen saturation in the blood of the internal jugular veins was 24 per cent. or less. Second are those whose carotid sinus was involved and in whom there was no preliminary fall in blood-pressure. These had neither decrease in cerebral blood flow nor decrease in the oxygen saturation of the blood leaving the brain." In this respect, the unconsciousness resembles that of

cataplexy and reflex epilepsy. This type probably depends on a reflex neural mechanism. The authors discuss the possibility that even in unconsciousness of the anoxic type, "a (reflex) neuro-mechanism may be interposed which abolishes consciousness and postural reflexes as a means of avoiding more serious cerebral anoxemia. The loss of the standing posture and the compulsory cessation of exertion tend to improve the oxygen supply to the brain. Syncope may be a reflex which has survival value to the individual."

#### CAROTID SINUS SYNDROME.

—S. Weiss, R. B. Capps, E. B. Ferris, Jr., and D. Munro (Arch. Int. Med. 58: 407 (Sept.) 1936) discuss the occurrence of *syncope* and *convulsions* due to a hyperactive carotid sinus reflex. The carotid sinus is a small glandular body often containing chromaffin granules, situated at the bifurcation of the common carotid artery. Normally, pressure on this structure produces no reaction. In a hypersensitive state, pressure or massage may produce unconsciousness, convulsions, or milder manifestations. In such hypersensitive states, these symptoms may appear spontaneously. The reaction is mediated through one or more of 3 reflex arcs. The afferent and efferent arms are in the autonomic nervous system. Stimulation may be mechanical, by pressure, massage, or changes in the caliber of the carotid artery, or it may be hormonal, or due to other chemical substances. The chief afferent paths are the intercarotid, glossopharyngeal and hypoglossal nerves, as well as the vagus and cervical portion of the sympathetic. Along these paths the impulse reaches the brain stem and goes out by autonomic pathways which may vary. In man, they are probably the vagus nerve, vasomotor depressor nerves, central motor pathways or combinations of these.

**Types.**—The authors discuss 3 types of carotid sinus syndrome:

1. *Vagal Type.*—The symptoms of dizziness, fainting, and weakness are due to cardiac asystole, with sinoauricular or auriculoventricular block, producing cerebral anoxemia. Associated with this is a fall in blood-pressure. An attack may be produced by massaging the sinus against the cervical vertebra for 15 to 30 seconds. The attack can be abolished within 3 minutes by an intravenous injection of 1 mg. ( $\frac{1}{65}$  grain) of atropine sulphate, which produces paralysis of vagus endings. Eight minims (0.5 c.c.) of solution of epinephrine hydrochloride subcutaneously prevents an attack, through a local stimulating effect on the ventricles.

2. *Depressor Type.*—This is the least common, and is usually found associated with one of the other two types. The efferent impulse acts on the small blood vessels by way of the aortic depressor nerves. The symptoms arise from a primary reflex vasodilatation, and a secondary fall in blood-pressure, unrelated to cardiac slowing or any arrhythmia. However, there is a diminution in blood-flow to the brain, with resultant anoxemia. The attacks may be reproduced as in the first type. Atropine has no effect on the attack, but epinephrine prevents an attack by constricting the small blood vessels.

3. *Cerebral Type.*—In this type symptoms occur from impulses which apparently travel directly to the brain. There is no accompanying change in pulse rate or blood-pressure, and the total blood flow through the brain remains normal during unconsciousness. Apparently the pathway is from the medulla to vegetative centers in the hypothalamus, or to vessels supplying these centers. Attacks can be reproduced, usually quickly, as above, and subjective signs are prominent. Neither atropine nor epine-

phrine aborts or relieves this type. However, injection of the sinus with procaine hydrochloride makes the local stimulus ineffective.

**Clinical Features.**—The clinical manifestations of a hyperactive carotid sinus reflex are usually attacks of unconsciousness, with or without convulsions, occurring days to months apart. They are usually preceded by a sensation of dizziness, weakness, ringing in the ears, or epigastric distress. Occasionally, premonitory symptoms are absent. Between attacks there may occur minor episodes of dizziness, weakness, or numbness and tingling of the extremities. The attacks occur when the patient is upright, and are relieved by lying down. They may follow sudden movements of the neck, blows to the neck, or sudden elevation of the head. Fatigue, emotional upsets, and menstruation may be contributing factors. The unconsciousness usually lasts 1 to 3 minutes, and the patient feels well afterwards, except for some headache or continued dizziness. The following manifestations may be present in an attack: hyperpnea or apnea, pallor, bradycardia, numbness and tingling of extremities, convulsions, drowsiness, cataplexy, epigastric distress, nausea, lacrimation, cough, amnesia, palpitation.

In most patients, local lesions or generalized disease are found. In 7 of 17 subjects of the vagal type of attack, there was evidence of degenerative changes in the heart, and in the group as a whole there was a high incidence of cardiovascular change. Too much digitalis may be a factor, and the authors urge against its routine preoperative use unless there is definite evidence of cardiac failure. The digitalis, plus a volatile anesthetic, plus manipulation around the neck by the anesthetist, are likely to produce vasomotor collapse, cardiac arrhythmia, and even sudden death.



In most of the cases with hyperactive carotid sinus reflex, various grades of neurosis are present. They often show a low basal metabolic rate which is not due to hypothyroidism. In general, the vagal and depressor types predominate in patients with degenerative disease, and these two are equally distributed in patients with neurosis. A mild neurosis is frequently present in patients with the cerebral type.

**Diagnosis.**—The diagnosis of a hyperactive carotid sinus reflex is made on the occurrence of short attacks of syncope and related manifestations, usually developing when the patient is upright and reproduced by mechanical stimulation of the sinus. This is done by having the patient sit or stand upright, with the head well back, and pressing at the carotid bifurcation on one side against the cervical vertebra. Injection of the sinus with 1 per cent. procaine hydrochloride prevents an induced attack. The attacks may simulate atypical *petit mal*, *grand mal*, *narcoleptic* or cataleptic fits. There is no relation to epilepsy or postural hypertension.

**Treatment.**—It is essential to look for local or generalized disease conditions, fatigue, worry, etc. It is also essential to reassure the patient that this is not heart disease. For the *vagal type*, atropine sulphate, 0.5 mg. ( $\frac{1}{120}$  grain),

3 to 4 times daily by mouth, should be given or its equivalent of **tincture of belladonna**. The smallest amount necessary should be used. If the side effects are uncomfortable, **ephedrine sulphate**, 30 mg. ( $\frac{1}{2}$  grain), 3 times daily, should be given after meals. This acts on the ventricles. If this produces excessive nervousness, 15 mg. ( $\frac{1}{4}$  grain) **phenobarbital** with each dose. Surgical denervation may finally be necessary.

For the *depressor type*, 15 mg. ( $\frac{1}{4}$  grain) **ephedrine sulphate**, 3 to 4 times daily is indicated. **Surgery** may be necessary.

If general care and correction of the accompanying conditions are insufficient in the *cerebral type*, then **surgical denervation** is indicated, especially if the attacks seriously impair the patient's usefulness.

Following the operation, there is an increase in the blood-pressure and pulse rate, but this lasts only 2 to 6 hours. The authors state that in 10 cases of operative interference, only 2 had a recurrence of symptoms, and these two patients had basal metabolic rates of -20 per cent. and -25 per cent., with stigmata of severe vegetative neuroses. Those patients who had a basal metabolic rate from 0 to -11 and a slight neurosis remained free from attacks after operation.

## ENCEPHALITIS

By HENRY A. DAVIDSON, M.D.

The problem of encephalitis has many angles, all of which are still enshrouded in mystery in most respects. The tendency is to regard encephalitis in a very broad sense. There have been several classifications in the past few years in order to clarify this most perplexing group of disorders. All of them are similar in most details, only the termin-

ology varying among the various investigators. A useful grouping is the following: (1) *polioencephalitis vera*, including poliomyelitis, epidemic encephalitis, rabies, and herpes zoster; (2) acute demyelinating types, including acute disseminated encephalomyelitis, acute multiple sclerosis, and neuromyelitis optica; (3) diffuse perivenous en-

chepalomyelitis, such as those occurring after measles, chickenpox, smallpox, mumps, and vaccination; (4) polioencephalitis of the syphilitic type; (5) meningoencephalitis occurring in tuberculous and purulent meningitis; (6) metastatic encephalitis, such as occurs in blood stream infections, subacute bacterial endocarditis, and other disorders; (7) "hemorrhagic encephalitis" occurring in trauma and toxic disorders of various sorts; (8) toxic encephalitis.

Certain forms of encephalitis seem to be more common now than formerly. In the last few years, there has occurred the St. Louis outbreak of encephalitis, probably due to a virus. It is stated that sporadic forms of encephalitis are more numerous than in previous years. Little has been added to knowledge of the diagnosis or symptomatology of encephalitis except to indicate, what has been known for some time, that the clinical manifestations are very varied.

The *etiology* of most of the forms of encephalitis is still obscure. There is a general tendency to regard many as due to viruses. The problem of the etiology of the postvaccinal and measles types is still not settled. It is not certain whether these are due to a virus or to a bacterial agent presumably activated by the diseases in question.

The only real advance in the *treatment* of the postencephalitic disorders lies in the **atropine** treatment of *parkinsonism*. **Quinine** has been advocated for *multiple sclerosis*, but the results are not definite. The treatment of the *acute encephalitides* is for the most part **symptomatic**.

**THE VIRUS.**—The virus of the St. Louis type of encephalitis was isolated by C. Armstrong and R. D. Lillie (Pub. Health Rep. 51:1069 (Aug. 7) 1936) and inoculated into mice. They produced a destructive inflammation of the gray matter in the brains of the animals.

The same experiment was also performed for the virus of Japanese Summer Encephalitis, by H. Hashimoto, M. Kudo and K. Uraguchi (J. A. M. A. 106:1266 (Apr. 11) 1936) with similar effects. When they used partly immunized mice, Armstrong and Lillie found that a myelitis rather than an encephalitis developed. Although this might mean that the spinal cord cells are more sensitive than cerebral neurones, the authors are inclined to interpret it as meaning rather that the immunization process is more effective on brain cells than on those of the spinal cord.

Evidence that the common oriental mosquito, *Aedes albopictus* Skuze, can and does transmit the virus of equine encephalomyelitis is found in the observation of J. S. Simmons, F. H. K. Reynolds and V. H. Cornell (Am. J. Trop. Med. 16:289 (May) 1936) that the disease can be reproduced in a guinea-pig which is bitten by a mosquito that had previously fed on an infected animal.

**POSTVACCINIAL ENCEPHALITIS.**—The mechanism of encephalitis which occasionally follows vaccination has not been explained, but presumably it might be due to an accidental impurity in the vaccine, an immunologic response to the foreign protein, or to the transmission of some bovine virus. On the basis of the bacteriologic evidence uncovered at an autopsy, L. Heerup (Hospitalstid. 79:169 (Feb. 18) 1936) suggests that the complication is associated with severe infection in the upper respiratory tract. He states that the vaccine virus might always cause encephalitis were it not for the effects of the reticulo-endothelial system, which successfully checks the influence of the virus. In the presence of a serious infection, the barrier effects of the reticulo-endothelial system are impaired. This may occur in an apparently healthy child

who has a latent infection. In the case cited, the patient had a staphylococcic sore throat. He developed encephalitis following smallpox vaccination, and at autopsy a hyperplasia of the spleen, thymus, lymph nodes and other parts of the reticulo-endothelial system was found, accompanied by a staphylococcic invasion of the lungs and a diffuse perivascular degenerative lesion in the brain.

**NONSUPPURATIVE ENCEPHALITIS.**—Acute nonsuppurative encephalitis usually occurs in association with *intoxications* (such as arsenic or lead poisoning) or *infections*, particularly of exanthematous form (such as measles). The characteristic clinical picture is that of a general infection, *i. e.*, headache, vomiting, and fever, combined with signs of cerebral involvement, such as convulsions, confusion, or drowsiness. Pathologic findings include engorgement of the meningeal vessels, destruction of nerve tissues, and hemorrhages into the gray matter. Five cases are reported by R. J. Shafer (J. A. M. A. 106:699 (Feb. 29) 1936) with only 1 death. The fatality occurred in a pregnant woman, and the etiology was undetermined, although presumably some toxemia associated with the pregnancy was the responsible factor. One of the patients developed encephalitis in connection with a throat infection, and in the other three cases, measles preceded the cerebral involvement. In two of these, intramuscular injections of the citrated blood of persons who had had measles were given. No specific treatment was attempted in the third case, and all three made equally good recoveries. Spinal fluid examinations disclosed a lymphocytosis in all five cases.

The type of encephalitis occurring periodically during the summer in Japan appears to be clinically, epidemiologically, and pathologically similar to the St. Louis form. H. Hashimoto, M. Kudo

and K. Uraguchi (*Med. J.* 1940: 1296 (Apr. 11) 1936) report several cases in occidentals living in Japan. The onset was abrupt with severe headache, fever, and varied neurologic signs, such as trismus, stiff neck, and mental disturbances. No instances of diplopia were found. The acute illness ran a course of 5 to 10 days, and most of the patients got well. A spinal fluid lymphocytosis was the rule. The disease could be reproduced in mice by the intracerebral and intraperitoneal inoculation of emulsions made from the brain tissue of humans who had died from the disease.

Ten cases of encephalitis developing after *measles* are reported by J. Chalié, M. Plauchu, and L. Badinand (J. de méd. de Lyon 17: 579 (Sept. 5) 1936), who find that the complication usually does not appear until after subsidence of the measles exanthem. They also find a lymphocytosis in the spinal fluid. A case in which a spinal fluid examination disclosed a polynucleosis rather than a mononucleosis is reported by S. Hirsch (Med. Rec. 144: 310 (Oct. 7) 1936), whose patient had an encephalitis of undetermined origin, with headache, vomiting, fever, eye-ache, and stiff-neck. Following **lumbar puncture**, the symptoms receded, and the patient had completely recovered by the sixth day. This seems to indicate that an encephalitis with an increase in the number of polymorphonuclear cells in the spinal fluid is not always more grave than cases in which the lymphocytes predominate.

**CHRONIC ENCEPHALITIS, PARALYSIS AGITANS AND OTHER POSTENCEPHALITIC SEQUELS.**—*Treatment.*—The **Bulgarian treatment of Parkinsonism** consists in the use of large doses of atropine or belladonna. Excellent results in the treatment of 5 patients by this technic are reported by C. Bonorino Udaondo (Prensa méd. argent. 23: 1355 (June 3)

1936). The schedule suggested by H. Weber (Med. Welt 10:1038 (July 18) 1936) begins with a dose of 0.25 mg. ( $\frac{1}{250}$  grain) of **atropine** in tablet or liquid form, 3 times a day. The total daily dosage is increased by 0.25 mg. ( $\frac{1}{250}$  grain) daily until no further progress is made. This is usually reached with a dosage of 2 to  $2\frac{1}{2}$  mg. ( $\frac{1}{32}$  to  $\frac{1}{25}$  grain), 6 to  $7\frac{1}{2}$  daily. Excellent clinical results are reported, with no serious evidences of toxic accumulation. Similarly good results following the Bulgarian treatment were found by A. d'Ormea and E. Broggi (Rassegna. di studl. psichiat. 25:125 (Mar.-Apr.) 1936), who used a 5 per cent. decoction of **Atropa belladonna** in white wine. For adults the dose was 15 c.c. ( $\frac{1}{2}$  ounce), 3 times a day.

The treatment of victims of *paralysis agitans*, by the intravenous injection of **sodium iodide** (according to the Economo technic) was successful in one-half of the patients treated in a series reported by A. Olsen (Ugesk. f. laeger 98:180 (Feb. 27) 1936). While no danger can result from the treatment, some patients may be too sensitive to

iodine compounds to tolerate the medication.

The psychic phases of *paralysis agitans* are stressed by W. Marshall (J. Nerv. and Ment. Dis. 84:27 (July) 1936). He instituted **exercises** in relaxation and in **reëducation** of the rigid or tremulous limbs. Continuous reassurance of the treatability of the condition had to be given, and the attitude of despair and invalidism was relieved by **psychotherapy**. Good results are reported, which, in the author's opinion, are due largely to the mental catharsis associated with the psychotherapy.

Some success in diminishing the tremor of *paralysis agitans* was found by G. Pitorowski (Med. Rec. 144:322 (Oct. 7) 1936), who used intravenous injections of **methylene blue**. A 1 per cent. solution in distilled water is used. The initial dose is 5 c.c. ( $1\frac{1}{4}$  drams), but this is gradually raised to 10 c.c. ( $2\frac{1}{2}$  drams). The injections should be given twice a week for several weeks. By raising the tonus of the parasympathetic nerves and diminishing muscle tone, the drug is able to reduce the intensity of the tremor in some cases.

## ENCEPHALOGRAPHY AND VENTRICULOGRAPHY

By ELI MARCOVITZ, M.D.

**TECHNIC.**—The technique of encephalography has been modified in the past few years. Partial encephalography, consisting of the introduction of only small amounts of air, has been used with good results and does away with severe after-effects. The latter have also been eradicated to a large degree by the inhalation of 95 per cent. **oxygen** after the completion of the encephalogram pictures, the air being replaced by oxygen which is less irritating and absorbed much more quickly than air. The reading of encephalograms

has been aided materially by a recognition of the normal structures in the air pictures. (Dyke and Davidoff.)

The reduction of postencephalographic symptoms by the inhalation of 95 per cent. **oxygen** has been advocated by R. S. Schwab, J. Fine, and W. J. Mixter (J. Nerv. and Ment. Dis 84:316 (Sept.) 1936). The severe headaches and shock following air injection are completely done away with by the inhalation of 95 per cent. oxygen for  $\frac{1}{2}$  to 2 hours. The air is replaced by this means by the less-irritating oxygen.

T. J. C. von Storch (Brain 59:250 (June) 1936) discusses the clinical application of the craniovertebral dynamics to encephalography. He believes that "(1) a complete lumbar puncture study should be performed previous to encephalography, and the pressure in the recumbent position recorded for use during encephalography. The studies of the dynamics, cytology, chemistry and serology of the cerebrospinal fluid may contraindicate or render unnecessary the subsequent encephalography. (2) Encephalography is contraindicated in the presence of a lumbar cerebrospinal fluid pressure in the recumbent position greater than 200 mm. of water or when signs of increased intracranial pressure are apparent. It is dangerous when weak-walled anomalies of the cerebral vascular bed are present. (3) Anesthesia or deep narcosis is an aid to patient and operator. Inhalant anesthetics produce a dilatation of cerebral vessels increasing the pressure and preventing adequate filling, and are, therefore, contraindicated." He has used **avertin**, 100 mg. ( $1\frac{1}{2}$  grains) per kilo ( $2\frac{1}{5}$  lbs.) body weight per rectum, or **nembutal**, 3 to 10 grains (2 to 6 Gm.), intravenously, with less severe subsequent reactions than in unanesthetized patients. He recommends some form of simultaneous replacement of fluid by air, by a double puncture needle or by 2 punctures, to prevent alterations of intracranial pressure. "All obtainable cerebrospinal fluid should be replaced by a volume of gas which produces a lumbar subarachnoid pressure in the *sitting* position approximating to the previously recorded lumbar pressure for that patient in the *recumbent* position. In order to do so it is usually necessary to introduce a volume of air greater than the volume of fluid it replaces. . . . During replacement the patient's head should be slowly and continuously antero- and postero-flexed

in order to evacuate the ventricles. Lateral flexion is contraindicated as it predisposes to unequal distribution of the supracortical air."

Von Storch concludes that "(1) the cranio-vertebral container of the cerebrospinal fluid system of man is semi-rigid. (2) The cerebrospinal fluid system is subject to pressure alterations dependent upon its angle from the horizontal and upon pressure changes in its vascular components. (3) The lumbar cerebrospinal fluid pressure measured with the patient sitting up closely approximates the vertical cisternolumbar distance for that patient, and bears no relation to the pressure measured in the recumbent position. (4) Since the elasticity of the craniovertebral system is an individual variant, volumetric computations cannot be used as indices of expected pressure changes occurring in the ventriculosubarachnoid spaces. Observations of such pressures must be made directly. (5) Replacement of cerebrospinal fluid (by syringe) through a single lumbar puncture produces alternate elevation and depression of the cerebrospinal fluid pressure. Simultaneous replacement of cerebrospinal fluid prevents these alternations and minimizes the patient's unfavorable reactions. (6) When the cerebrospinal fluid has been completely replaced by gas, the ventriculosubarachnoid space is a gas-filled system in which pressures at all points are equal irrespective of position. Therefore, the lumbar subarachnoid pressure in such a system remains the same whether the patient be sitting or recumbent, and consequently the intracranial pressures are unchanged. (7) The production of a final lumbar subarachnoid pressure, after complete replacement of the cerebrospinal fluid by a gas, which approximates the normal lumbar cerebrospinal fluid pressure for that patient when recumbent is not

dangerous. It results in excellent roentgenograms under normal pressure-volume relationships and does not increase the patient's reaction. (8) It is possible to introduce a volume of air at room temperature (20° C.) greater than the volume of cerebrospinal fluid removed (at 37° C.) without significantly increasing the intracranial pressure. (9) The introduction of a volume of air greater than the volume of fluid it replaces increases the reliability of the encephalograms. (10) Subsequent to encephalography, after the manner outlined, the cerebrospinal fluid pressure is not increased above its normal value. The untoward reactions occasionally occurring are not due to increased intracranial pressure."

**Subdural Air.**—F. Lemere and C. H. Barnacle (Arch. Neurol. and Psychiat. 35:990 (May) 1936) reviewed 800 encephalograms with special reference to the occurrence of subdural air, and nonvisualization of the ventricles. They found that 20 per cent. of the encephalograms showed air in the subdural space. The presence of subdural air was subsequently demonstrated by trepanation in 1 case and by postmortem examination in 2 others. In this series, the amount of fluid removed during the procedure apparently had little relation to the presence of subdural air or to the severity of the postoperative reaction. However, the postoperative reactions were about twice as severe and the mortality rate was over twice as high in patients showing subdural air as in those showing air in the subarachnoid space. The authors believe that the entrance of air into the subdural space may be associated with an underlying cortical atrophy or may be due to a technical error. The latter condition is more likely when air in the subtentorial space and collapsed ventricles are also present. In the opinion of the

authors, air probably enters the subdural space through tears in the arachnoid membrane, and extensive manipulation of the head during the procedure may increase these tears. The ventricles were not visualized in 8 per cent. of this series, and this was noted twice as frequently in cases in which air had entered the subdural space as in cases in which it had entered the subarachnoid space.

**Diagnosis.**—E. P. Pendergrass and P. J. Hodes (Radiology 26:146 (Feb.) 1936) point out the value of reëxamining every patient with poor ventricular filling 24 hours after the original encephalogram. As a rule, the 24-hour examination yields little additional information. In the occasional case, however, it is of inestimable value.

C. G. Dyke (Bull. Neurol. Inst. of New York 5:135 (Aug.) 1936) presents what he considers a pathognomonic encephalographic sign of *subdural hematoma*. This consists of a large finger-like collection of air over the hemisphere, projecting diagonally, ventrally and laterally from the midline. "In the anteroposterior views the lateral surface appeared convex superiorly and concave ventrally, but when studied stereoscopically, there was actually a concavity superiorly and laterally in the anteroposterior plane. It was felt that the air was between the arachnoid and inner membrane of a subdural hematoma." This unusual picture occurred in 1 of 5 cases of confirmed hematoma which had been examined by encephalography.

C. G. Dyke and L. M. Davidoff (*Ibid.* 4:602 (Apr.) 1936) present criteria for the diagnosis of *tumors of the corpus callosum* by means of encephalography. They state that the characteristic findings are "(1) Separation and asymmetrical distortion of the lateral ventricles; (2) a sharp defect in the dorsal margin of one or both lateral

ventricles; (3) occasional failure of one lateral ventricle to fill with gas; (4) distortion of the sulci and convolutions on the medial aspect of the brain; and (5) deformity or obliteration of the dorsal and rostral part of the third ventricle. . . . Furthermore, confirmation not only of the presence, but also of the size of the tumor may be gained from the degree of distortion and displacement of the lateral and third ventricles and cingulate and callosal sulci." The picture may be confused with (1) cyst of the cavum septi pelucidi, (2) agenesis of the corpus callosum, (3) intraventricular tumors, and (4) parasagittal tumors. Cysts of the cavum septi pellucidi also produce a separation of the ventricles, but their mesial margins are concave, smooth and symmetrically affected," and in the lateral views the defects in the dorsal margins of the ventricles are never found.

In agenesis of the corpus callosum "the lateral ventricles are also separated from each other, and the mesial borders are concave." "The dorsal margins of the lateral ventricles are characteristically pointed in the anteroposterior views. In these views the interventricular passage is elongated and the third ventricle extends dorsally between the shadows of the lateral ventricles. In the lateral views the caudal portions of the lateral ventricles are dilated and the frontal horns may be undeveloped. The sulci on the medial aspect of the brain course ventrodorsally through the zone normally occupied by the corpus callosum, rather than horizontally. Furthermore, in the plain x-ray picture of the skull, evidence of increased pressure is absent in cases with the congenital lesion and is often present in the case with tumor."

Differentiation from *tumors within the lateral ventricles* can be made on the fact that these "usually deform only a

single ventricle, and furthermore, they encroach upon the ventral aspect of the ventricular cavity rather than the dorsal one."

*Parasagittal tumors dorsal to the corpus callosum* produce a diffuse flattening and depression of the hemilateral ventricle, and the ventricles are never separated, but may be displaced together to the opposite side.

L. M. Davidoff and C. G. Dyke (*Ibid.* 4: 221 (Oct.) 1935) present 9 cases of *congenital tumors within the third ventricle* which were diagnosed by encephalography or ventriculography. The criteria which they found to indicate the presence of a tumor in the anterior portion of the third ventricle are:

I. In the *encephalogram* (*a*) usually symmetrical dilatation of the lateral ventricles, which are in their normal position; (*b*) filling defect in the anterior portion of the third ventricle; (*c*) a concave or straight margin to the anterior border of the air caudal to the filling defect; (*d*) normal sized or slightly dilated aqueduct of Sylvius and fourth ventricle if visualized; (*e*) incomplete filling or deformity of the cisternæ interpeduncularis and pontis; (*f*) dorsal displacement of the medial cerebral sulci.

II. In the *ventriculogram*:

A. With unilateral puncture: (*a*) the failure of air to pass at all or with difficulty into the other lateral or third ventricle; (*b*) the deviation of the septum pellucidum to either side; (*c*) and (*d*) as above, in encephalogram.

B. With bilateral puncture: (*a*) bilateral symmetrical dilatation of the lateral ventricles, which are situated in their normal position; (*b*) cutting off of the air shadow in the foramen of Monro; (*c*) and (*d*) as above.

They also add that a defect in the septum pellucidum can be diagnosed by the absence of the shadow of the septum

in the anteroposterior view and a fusion of the lateral ventricles across the midline.

**Thorium Dioxide.**—W. Freeman, H. H. Schoenfeld and C. Moore (J. A. M. A. 106:96 (Jan. 11) 1936) discuss the use of colloidal thorium dioxide as a means of delineating the ventricular system. They inject 3 c.c. into each ventricle through a burr-hole, mixing it with the ventricular fluid by back-and-forth movements of the piston of the syringe. The authors believe "that colloidal thorium dioxide is of great value

as a contrast medium for ventriculography. It is freely miscible with the ventricular fluid, is of high specific gravity, finding its way into the recesses of the ventricular system, and on account of its high radiopacity needs to be used in relatively small amounts. It is eliminated, in normal cases, within 4 hours and is so inert that it provokes only a mild inflammatory reaction. Most important of all, it preserves the supporting fluid cushion of the brain and avoids the serious constitutional effects of air ventriculography."

## EPILEPSY AND THE CONVULSIVE STATE

By HENRY A. DAVIDSON, M.D.

**Physiology.**—S. Weiss, R. B. Capps, E. B. Ferris, Jr., and D. Munro (Arch. Int. Med. 58:407 (Sept.) 1936) point out that epileptiform seizures may be due to *stimulation of a hypersensitive carotid reflex*. This is associated with a lowering of the cerebral blood-pressure. Sometimes, mechanical stimulation of the carotid sinus may precipitate a paroxysm. Even the administration of digitalis may sensitize the carotid mechanism sufficiently to provoke a convulsion. Whether hypoglycemia is a factor in the production of epileptiform spells is unsettled, but the experiments of E. Ziskind (Arch. Neurol. and Psychiat. 36:331 (Aug.) 1936) seem to indicate that it cannot play a large rôle. Among 40 epileptics, he was unable to induce a single convulsion by the injection of insulin, although in some cases he used as much as 60 units. On the other hand, he was able to produce spells in 4 out of 31 epileptics by administering large quantities of *water*.

Reflex epilepsy cannot be induced merely by the application of a stimulus. Some "convulsive tendency" in the brain is necessary. In the presence of this

tendency, however, almost any stimulus, *i. e.*, heat, cold, trauma, electricity, etc., may induce an attack. W. Baumann (München. med. Wchnschr. 83:841 (May 22) 1936) was able to elicit spells in sensitive patients by using *cold* as a stimulus. This was secured by the application of an *ethyl chloride spray*. A case of reflex epilepsy in which *bright light* was the stimulus is recorded by R. Goodkind (Arch. Neurol. and Psychiat. 35:868 (Apr.) 1936). In this case exposure to bright sunlight could produce an attack if the eyes were left uncovered, but when the patient was blindfolded, no intensity of light could provoke a seizure. Nor could exposure to ultraviolet rays induce a paroxysm, even with the eyes open. The presence of fixed pupils during the attack, seemed to rule out hysteria. Apparently in this case of reflex epilepsy, the retina was the sensitive zone. That the patient already had the "convulsive tendency" required by Baumann, was indicated by a history of convulsions for 6 years before the first evidence that the fits would be precipitated by bright light.



**Diagnosis.**—Two approaches are available in making an objective diagnosis of epilepsy: One relies on certain specific signs, such as the Babinski or on pupillary changes; the other seeks to provoke an attack so that the physician may observe the spell. Using the former method, G. Stiefler (Klin. Wchnschr. 15:16 (Jan. 4) 1936) suggests that the absence of the basal joint reflex (reflex of the proximal phalanx) may be valuable in distinguishing epileptic from hysterical convulsions. The response is elicited by bending to maximum passive flexion, the metacarpophalangeal joint of the second or third finger. The reaction is positive when, as a response to this procedure, the terminal phalanx of the thumb extends, while the basal segment flexes. This response, normally present in most healthy adults, is absent in epilepsy. Of course, the examiner must be certain that a positive reaction can be secured during the normal intervals between spells in the patient under study. If this is so, its absence during a fit is indicative of the truly epileptic nature of the paroxysm. To bring on a convulsion, U. Moeller (Jahrb. f. Kinderh. 146:240 (Apr.) 1936) suggests 3 technics: (1) hyperventilation, (2) injection of pituitary solution, and (3) alkalization. The latter is effected by administering *sodium potassium citrate* until the urine is rendered alkaline. For injection, solution of the *posterior lobe of the hypophysis* is used. In a series of 121 children subject to convulsions, it was impossible to precipitate a spell by any of these methods, in 78; of the remaining 43, the paroxysm was of the "salaam convulsion" type, in 8 cases. In 14 of the remaining 35 cases, pyknoleptic spells were produced. Pituitary was more likely to bring about a salaam convulsion than either of the other 2 technics; hyperventilation was the most successful method of provoking

pyknoleptic episodes. In children with ordinary idiopathic *grand mal*, alkalization was the effective method of eliciting the fit. Moeller suggests that by using these tests, it should usually be possible to bring about the attack and to indicate its nature.

Epileptiform seizures are occasionally caused by infestation of the brain with the *cysticercus*. A case is cited by I. H. Perry (Arch. Neurol. and Psychiat. 35:862 (Apr.) 1936) in which a patient, 50 years old, with a history of long-standing intestinal tapeworm, had been having right-sided convulsions for 15 years. Autopsy disclosed multiple cysts of the *cysticercus cellulosæ* in the brain. A large one, apparently accounting for the spells, was found in the left motor area. The condition is rare, but should be thought of in patients with convulsions who present an eosinophilia, a history of tapeworm, cysts in the subcutaneous tissues, larvæ in the spinal fluid, or x-ray evidence of calcified nodules in the head.

Epileptiform attacks may be the first evidence of *brain tumor*. Reviewing 300 cases of *glioma* of the cerebral hemispheres, C. F. List (*Ibid.* 35:323 (Feb.) 1936) finds a history of seizures in about half the cases. Generalized convulsions occurred when the tumor was in the frontal or temporal region more often than when it occurred elsewhere. *Petit mal* attacks were more likely to point to lesions of the temporal, temporo-occipital, or temporo-frontal areas. Sensory auras, Jacksonian fits, and other specialized types of seizures usually indicated the site of the neoplasm on the basis of the generally accepted views of cerebral localization. Convulsions were more frequent in slow-growing than in fast-growing tumors. Spells were more common in infiltrating than in well-demarcated neoplastic processes. The size of the mass exercised no in-

fluence on the presence, absence, or frequency of the paroxysms. Patients with epileptiform episodes lived longer than did those without such symptoms, so that the attacks may be considered a somewhat favorable prognostic sign.

**Treatment.**—Good results in the x-ray treatment of 66 epileptics are reported by M. Sgalitzer (Fortschr. a. d. Geb. d. Röntgenstrahlen 53:580 (Mar.) 1936) who radiated the forehead, right and left lateral, and occipital fields. He used 4 portals, each 6 x 11 cm. in size, and employed a heavy filter. A dosage of from 75 to 90 r is used on the first day, and thereafter daily for 1 or 2 weeks. Each field should not receive more than 270 r. From 6 to 8 weeks later, the entire series is repeated. A third series may be given later in the year if indicated. The x-rays seem to influence the production of cerebrospinal fluid, and to exercise some effect on the large cerebral vessels.

Many surgical procedures have been proposed, both for Jacksonian and idiopathic epilepsy. Among these are **cervicothoracic sympathetic gangliectomy** and **denervation of the carotid sinus**. W. Penfield (Arch. Neurol. and Psychiat. 36:449 (Sept 1936) condemns both of these operations as unjustified except in extremely unusual cases. Except when there is a chronic collection of fluid in a subarachnoid space. Penfield believes that **subtemporal decompression**, as a primary operation is futile, although it may be necessary as a step in other craniocervical procedures. In children with recent epilepsy, **spinal insufflation of air** may be effective. In cases of *Jacksonian epilepsy*, surgery has more to offer, and if cicatrices, tumors, or areas of focal atrophy can be demonstrated, their excision is usually justified. In operating on a brain to relieve convulsions, the surgeon should cut his line of excision

through the adjacent healthy cerebral tissue to discourage scar formation.

On the theory that epileptics have a cerebral anoxemia, W. G. Lennox and A. R. Behnke (*Ibid.* 35:782 (Apr.) 1936) experimented with the effect on patients of increased **oxygen pressure**. That anoxemia does exist seems established by a study of 88 epileptics made by W. G. Lennox and E. L. Gibbs (*Ibid.* 35:1198 (June) 1936), who found that in one-half of these patients the oxygen saturation of the blood tended to be below normal. To determine the effect of decreased pressure, Lennox and Behnke placed 3 patients suffering from *petit mal* in a **compression chamber**, where they remained for from 3 to 5 hours at a time under an absolute pressure of 4 atmospheres. The average number of attacks had been 1.4 per hour prior to the experiment, but for the time spent in the compression chamber, this average fell to 0.8 per hour. However, because of the damaging effect which pure oxygen may exert on the lungs, the authors doubt the clinical value of this procedure in the routine treatment of epilepsy.

J. E. Scarff (*Ibid.* 36:373 (Aug.) 1936) was able to relieve 3 patients suffering from a congenital, slowly progressing, paroxysmal disorder, with slight atrophy of an extremity. These attacks were first localized to the affected limb, but later became generalized. Trephine revealed in each case, a Pacchionian granulation attached to the motor gyrus. The **veins** which passed through this granulation running from the cortex to the superior longitudinal sinus were **doubly ligated and divided**, and the **granulations** were **coagulated**. The spells were substantially and enduringly relieved. Two of the patients had rare, transient, mild *petit mal* attacks after the operation, but were free of major spells. In the other pa-

tient, no seizures of any sort occurred after the lysis of the granulations.

**CONVULSIONS. — Pathogenesis.** — Because of the frequency with which epilepsy begins at the time of puberty, J. J. H. M. Klessens (Nederl. tijdschr. v. geneesk. 80: 1119 (Mar. 14) 1936) suggests that the internal secretions of the *gonads* may be related to the pathogenesis of the disorder. Since epilepsy rarely begins after the onset of puberty, it would appear as if the mature gonad cells check the irritability of the cerebral neurones. A somewhat similar viewpoint is presented by A. W. Pigott (J. M. Soc. New Jersey 33: 86 (Feb.) 1936), who suggests that the menstrual period is likely to be associated with instability of the central nervous system, and that this instability, combined with a preëxistent "convulsive state," may be responsible for the disproportionate frequency of paroxysms during the menstrual period.

Pigott also considers other endocrinologic aspects of the convulsive state. The *pineal* may be associated with spells when a neoplasm develops at the epiphysis, causing cerebral irritation. The pituitary plays a rôle in water metabolism, and the significance of hydration

and its effect on the convulsive state is well known. Pitressin, which is the anti-diuretic principle of posterior pituitary, is useful in inducing the positive water balance which may bring on spells. The solution of posterior pituitary is used by Moeller (see above, under "Diagnosis") to provoke paroxysms. The *thyroid gland* is occasionally a factor, Pigott has found many epileptics with hypothyroidism, but none with increased thyroid activity. The *parathyroid glands* are not as significant in the physiology of convulsions as might be expected from their effect on calcium balance and their part in tetany. Pigott found no abnormal concentrations or deficiencies in the blood calcium of epileptics. The endocrine secretion of the *pancreas* is probably a potentially epileptogenic agent. Pigott found that in most epileptics the blood sugar was lower during convulsions than between spells. In this, he differs sharply from E. Ziskind (*loc. cit.*) (reported above under "Physiology") who could find no significant relationship between hypoglycemia and epilepsy. Pigott also stresses the fact that among epileptics, diabetes is only one-seventh as common as it is in the general population.

## MENINGITIS

By HENRY A. DAVIDSON, M.D.

**MENINGOCOCCIC MENINGITIS. — Epidemiology.** — The effectiveness of broth filtrates of meningococcus culture in testing for sensitivity to the organism and in immunizing against the development of the disease is indicated in the report of D. M. Kuhns (J. A. M. A. 107: 5 (July 4) 1936). The 1: 100 dilution of the filtrate of the broth culture, which had been inactivated by merthiolate, was used in skin testing in 2 camps in one of

which an epidemic was in progress. All of the subjects who subsequently developed the disease gave one plus or greater responses. On the other hand, none of the convalescents gave positive reactions, suggesting that the attack had conferred a real immunity. The full strength filtrate was subsequently used for the purpose of immunizing the subjects, and in the second camp where an epidemic was threatened by the outbreak of 2 cases, all of the positively

reacting campers were thus immunized. No cases of meningitis developed in the second camp after the institution of this procedure, and 4 months later only 2 per cent. of those who had, prior to immunization, given plus reactions, showed positive responses to the skin test. The test was likewise used with a group of 150 school children, 0.05 c.c. of the 1:100 filtrate being employed. Of these children, 10 per cent. gave one plus or greater reactions; and these were then immunized. Following retests, not one of the children manifested positive responses.

In spite of the progress thus being made in understanding the epidemiology of meningitis, G. Rake (Canad. Pub. Health J. 27:105 (Mar.) 1936) points out at least 4 unanswered questions. These concern the duration of the carrier state; the immunologic relationships between host and organism; the relative virulence of case and carrier strains; and the differences between the saprophytic and parasitic forms of the meningococcus.

**Treatment.**—On the theory that **x-rays** diminish choroid plexus secretion, reduce cerebrospinal fluid pressure, and exercise a direct and favorable influence on inflamed tissue, H. Hippe and U. Grüninger (Klin. Wchnschr. 15:304 (Feb. 29) 1936) have been using irradiation for the control of residual symptoms in cases of epidemic meningitis. They report good results, but suggest that the procedure must be supplementary to the standard **serum treatment**, and that it should be used only after the acute phases of the illness have subsided. The fields should be 8 x 10 cm. each, and irradiation should be applied daily for several successive days. The recommended constants are: filtration by 0.5 mm. of copper and 1 mm. of aluminum; distance of 30 mm., current at 6 ma., tension at 180 K. V. Each

field should receive from 120 to 150 r. Frontal, temporal, parietal, occipital and cervical fields should be radiated.

Reviewing 468 cases of hospitalized meningitis, C. J. Tripoli (J. A. M. A. 106:171 (Jan. 18) 1936) finds that the mortality rate in the meningococci group was 65 per cent. However, when a combined **cisterna and lumbar puncture** technic was used, the incidence of fatality was only 42 per cent. Introduction of the **serum** by lumbar puncture appeared only partly effective, because the pressure factors in the cerebrospinal system did not permit much of the serum to reach the brain. Tripoli recommends the "**modified Lyon**" **procedure**, which uses combined puncture. The patient lies on his side with the head of the table elevated. The cistern is tapped first, and then a lumbar puncture is performed. Fluid is permitted to escape through both needles. The serum is prepared by warming to body temperature and by adding to it a few drops of Dandy's phthalein indicator for subsequent identification. It is then introduced through the cisternal needle, while spinal fluid is still being extruded through the lower needle. At this point, the foot of the bed is raised to a level 6 inches above the head, and the serum is allowed to flow into the cistern until it appears through the lumbar needle. At the same time, intravenous and intramuscular injections of serum are administered.

Instead of the intracisternal or intraspinal routes, A. Hoyne (*Ibid.* 107:478 (Aug. 15) 1936) recommends placing reliance largely on the **intravenous method**. He found a mortality rate of only 15 per cent. when the intravenous route was used exclusively, as compared with a rate of 51 per cent. when intrathecal technics were employed. He also prefers **Ferry's meningococci antitoxin** to the standard antimeningococcus

serum. In either event, the serum or toxin is diluted with a 10 per cent. **dextrose-in-physiologic-saline solution**, to which from 5 to 15 minims (0.3 to 0.9 c.c.) of **epinephrine** have been added. After being heated to body temperature, the preparation is given intravenously by the gravity method at a rate of about 1 drop per second. The initial dose is from 150 to 300 c.c. of the serum or from 50,000 to 100,000 units of the antitoxin. If indicated, the injection may be repeated at 24-hour intervals. An urticarial rash, which is not of serious significance, usually develops.

**VIRUS MENINGITIS.**—A form of meningitis in which the clinical picture closely mimics cerebrospinal fever, but in which there is no apparent bacterial cause and in which the outlook is favorable, has been previously described under the name of "*serous meningitis*." E. Glanzmann and D. Heller (Schweiz. med. Wchnschr. 66: 541 (June 6) 1936) call attention to the increase in the lymphocytic cells in the spinal fluid in this condition. They find that the condition occurs chiefly in children, and advise frequent **spinal taps** accompanied by the oral administration of **aminopyrine** and **methenamine**. A similar condition is described by M. Terrien (Monde méd., Paris 46: 645 (Apr. 1) 1936), who reports a case in which ocular symptoms suggested encephalitis; the rest of the clinical picture, however, was that of a meningitis, and treatment with **Pettit's serum** was followed by uneventful recovery. Investigating 2 cases of "*serous meningitis*," G. M. Findlay, N. S. Alcock and R. O. Stern (Lancet 1: 650 (Mar. 21) 1936) were able to isolate from the spinal fluid a virus which produced a fatal meningitis when inoculated intracerebrally into laboratory animals. Finding this virus in many apparently

healthy rats and mice, they suggest that this form of meningeal involvement may originate in the virus of the animals, which they believe, is transmittable to man. This may account for the cases reported by T. F. M. Scott and T. M. Rivers (J. Exper. Med. 63: 397 (Mar. 1936), wherein 2 laboratory workers developed serous meningitis at about the same time, though they were working 75 miles apart. In these cases, a virus was extracted from the spinal fluid which was able to reproduce meningitis in mice.

#### **MENINGITIS IN NEWBORN.**—

Meningitis in the newborn presents features which make diagnosis difficult. Reviewing 21 cases, W. S. Craig (Arch. Dis. Childhood 11: 171 (Aug.) 1936) found that ocular disorders and restlessness were more common than the usual symptoms of meningitis. The portal of entry appears to be the skin, mucous membranes, or oronasal passages, since, as a rule, injuries or disorders in these tissues are found. The colon bacillus was the causative organism in most of Craig's cases. The meningitis simulates pneumonia or intracranial hemorrhage, and final diagnosis is possible only after examination of the spinal fluid. The danger of developing this condition can be reduced if proper attention is paid to the care of the skin, mouth, eyes, and of the oral and nasal passages.

#### **INFLUENZAL MENINGITIS.**—

Only 1 case of acute suppurating meningitis in 100 is due to the influenza bacillus. Since it produces the clinical picture of an ordinary meningococcic fever, the diagnosis of this form of meningitis must be made by bacteriologic examination. E. Bender and H. Bruns (München. med. Wchnschr. 83: 557 (Apr. 3) 1936) report 2 cases of influenzal meningitis, pointing out the great severity of the illness, and the

serious prognosis. They estimate a mortality rate of about 92 per cent. Search for the influenzal organism should be made when cultures grown on blood-free media remain sterile after 24 hours.

**DIPHTHERITIC MENINGITIS.**—The first case of meningitis due to the diphtheria bacillus reported in the English or American literature is recorded by F. G. Carlson and H. W. Morgan (J. A. M. A. 106:1164 (Apr. 4) 1936). Their patient, a 2½-year-old boy, had had otitis media for 10 days. Following a paracentesis of the ear drums, meningeal symptoms de-

veloped. The spinal fluid contained 20,000 cells per c.mm., and smears revealed the presence of a diphtheroid organism which, on culture, appeared to be the Klebs-Loeffler bacillus. Testing revealed that this was a virulent strain of the organism. Throat cultures were also positive for the Klebs-Loeffler bacillus. In spite of the intensive administration, intramuscularly, intraspinally, and intracisternally, of large doses of diphtheria antitoxin, the patient died. Autopsy disclosed a diffuse purulent meningitis covering the entire brain and spinal cord.

## MIGRAINE

By ELI MARCOVITZ, M.D.

**Etiology.**—W. Timme (Bull. Neurol. Inst. New York 5:437 (Aug.) 1936) believes that the anatomical relationships of the pituitary present a basis for practically all of the pressure symptoms seen in *pituitary migraine*. "The large variety of symptoms may be grouped into 3 large classes: (1) *direct*—those produced by pressure of an expanding pituitary gland within too small a sella turcica; (2) the *indirect*—those produced by the effect of the hypophyseal activity on the various organs and tissues of the body, including the metabolic as well as those affecting both the sympathetic and the central nervous system; and (3) the "*ausfallserscheinungen*"—those produced by the lack of pituitary control in hypoplasias, as the gland endeavors vainly to reach an activity produced by too great a demand upon it, thereby bringing from a latent state to a visible one such symptoms as allergic edemas, anginas, purpuras and hemorrhages."

**Physiology.**—P. Solomon (Arch. Neurol. and Psychiat. 35:964 (May) 1936) investigated the electrical resist-

ance of the skin by means of the psychogalvanic reflex as a means of measuring the activity of the sympathetic nervous system during migraine attacks and during their relief by ergotamine. In 7 patients with migraine, he found no significant change in the electrical resistance of the skin during the period of relief from a characteristic headache by the use of ergotamine. "In one case a similar lack of change was observed during the spontaneous disappearance and reappearance of the headache. In another a 'march' of neurologic symptoms during a typical headache was likewise unaccompanied with any change in the electrical resistance of the skin. In 4 control patients without headache ergotamine caused no change in the electrical resistance of the skin." He concludes, therefore, that migraine is not a disease caused by general sympathetic dysfunction.

H. A. Riley, S. E. Soltz, R. M. Brickner and C. C. Hare (Bull. Neurol. Inst. New York 4:442 (Dec.) 1935) studied a group of 26 patients with migraine by routine laboratory investiga-

tions of blood, urine, spinal fluid and gastric secretion. They found no consistent deviation from the normal, and no confirmation for the statements frequently made:

1. That a pentosuria may frequently be present.

2. That an eosinophilia can often be demonstrated.

3. That the cholesterin content is materially elevated.

4. That migraine is often associated with evidences of marked gastrointestinal disorders.

**Treatment.**—M. E. O'Sullivan (J. A. M. A. 107:1208 (Oct. 10) 1936) reports on the treatment of migraine with **ergotamine tartrate**. Ninety-seven patients received this treatment, which was administered for the relief of 1132 headaches. All but 8 of the 97 patients were benefited, and 1042 headaches were completely checked in 89 individuals. There was no difference in the action when given to men or women. The author has found that "once ergotamine tartrate has abolished an attack, it has never failed, in 2 years' experience, to check again a migraine headache in that individual if given in adequate dosage." It has been found that the amount of the alkaloid required to effect relief is directly proportional to the severity of the attack. Therefore, when the patient feels he is "in for a bad one," a slightly larger dose is recommended. In a few cases the headache returned from 12 to 24 hours after initial injection. A second injection always controlled these episodes. The author recommends that the drug be administered as early as possible when the patient feels that an attack is imminent. In this way, "the attack may be completely aborted by a smaller dose in much less time, and the untoward effects of the drug will be greatly lessened."

The method used is to inject hypodermically a trial dose of 0.25 mg. ( $\frac{1}{250}$  grain), and the effectiveness of this is used as an index to future medication. If this dose is well tolerated and terminates the attack within 2 hours, then the dosage is considered satisfactory. If after 2 or 3 hours the attack persists, or if after from 8 to 12 hours the attack returns, an additional 0.25 mg. ( $\frac{1}{250}$  grain) is administered, and for future attacks 0.5 mg. ( $\frac{1}{125}$  grain) is given. It is rare that more than this is required, and only on 3 occasions has 0.75 mg. ( $\frac{1}{80}$  grain) been used.

Oral medication has not given as good results. However, 31 of 45 patients were benefited. The author recommends sufficient tablet dosage, up to 5 tablets, be taken at the first sign of an attack. It takes longer to alleviate the headache and the tablets are less dependable in their action, but in many cases they are useful.

*Untoward effects* such as *nausea* and *vomiting* may be relieved by the injection of  $\frac{1}{100}$  grain (0.65 mg.) of **atropine**. *Muscle pains* sometimes occur, and can easily be controlled by the injection of **calcium gluconate**, 10 c.c. ( $2\frac{1}{2}$  drams) intravenously. Daily calcium therapy will diminish or prevent their recurrence.

W. G. Lennox and T. J. C. von Storch (*Ibid.* 105:169 (July 20) 1935) also have used **ergotamine tartrate** intravenously or subcutaneously in 120 cases of migraine. The usual dose was 0.5 mg.— $\frac{1}{125}$  grain (the contents of a 1 c.c. ampoule). In some cases, one-half or one-third of this dose was sufficient to stop the attack. They also recommend its use early in the attack. In a group of 89 cases, nausea occurred in 77 per cent., and vomiting in 60 per cent. Of the 120 patients, 107 obtained abrupt and complete relief. Nineteen patients had used the drug for more than a year

and all but one had obtained relief on each occasion.

S. E. Soltz, R. M. Brickner, H. A. Riley and L. A. Salmon (Bull. Neurol. Inst. New York 4:432 (Dec.) 1935) have compared the results of oral administration of **ergotamine tartrate**, **amniotin** and **phenobarbital** in migraine. The doses used were: ergotamine tartrate, 1 mg. ( $\frac{1}{65}$  grain) twice daily, oral amniotin, 5 c.c. ( $1\frac{1}{4}$  drams) daily, divided into 3 equal doses; phenobarbital,  $\frac{1}{2}$  grain (0.03 Gm.), 3 times daily. They found that oral ergotamine tartrate is effective in male adults with either simple or ophthalmic migraine and in children of either sex; all but one of the children in the series presented the ophthalmic type of migraine. It is also effective in adult females who suffer from the simple type of migraine, but no definite statement could be made as to its value in ophthalmic migraine occurring in adult females. It is useful in women who are in the menopause. Colored women respond well to this therapy. Oral amniotin was found to be frequently useful in women who suffer from either the simple or ophthalmic type of migraine. Apparently the existence of the menopause, whether natural or artificial, appears to

be immaterial in determining the response. No men or children received amniotin. With both ergotamine tartrate and amniotin, women who had never been pregnant responded better than others. Women whose migraine did not start until after their last pregnancy responded well to amniotin. The authors found phenobarbital helpful in a small group, among which the ophthalmic type predominated. They could find no facts connected with abnormalities of menstruation or of the sella turcica which appeared to have any relation to the success or failure of any of the forms of treatment.

R. W. Whitehead and E. E. McNiel (Am. J. Psychiat. 91:1275 (May) 1935) report on the use of **emmenin** (a substance closely related to theelin (amniotin or oestrogen) in 12 cases of migraine (11 female and 1 male). Of the 11 females, all but two showed a definite relationship of the attacks to the menses. In these 2 cases and in the male, negative results were obtained with emmenin medication. Of the other 9, relief was marked in 6 cases, and partial in 3 others. The authors used a dosage of 15 drops of emmenin 3 times a day by mouth.

## MULTIPLE SCLEROSIS

By ELI MARCOVITZ, M.D.

**Symptomatology.**—R. M. Brickner (Bull. Neurol. Inst. New York 5:16 (Aug.) 1936) criticizes the prevailing view that objective sensory disturbances are of little importance in the clinical picture of multiple sclerosis. In a study of 62 patients, he found subjective and objective sensory changes, often of advanced degree, to be of common occurrence and typical of the disease. More than 95 per cent. of his patients had both.

“The commonest objective defect is that dependent upon lesions of the dorsal columns. Definite, and frequently striking, impairment of the senses of vibration and of position and movement was found in 95 per cent. of patients. . . . Implication of the spinothalamic tracts occurred in 24 cases (38.7 per cent.) in the present series. Occasionally the resulting sensory changes were observed in small, scattered areas, but more often they were confluent and extensive in dis-



tribution. The disturbance was seldom severe. . . . Of the subjective changes, so-called 'numbness' was—most frequently encountered,—[and] was a first symptom in 15 of the 62 present cases. . . . Pain was also a part of the syndrome in almost 100 per cent. of the cases. Most commonly, it was limited to the joints of the lower spine and of the extremities. Its customary character was arthritic and muscular rather than radicular; it was frequently described as an ache, rather than as of a burning or lancinating nature."

Brickner also points out the occurrence of vesical symptoms in 53 of the 62 patients, and stresses the fact that "in 22 patients vesical symptoms, of fairly great intensity, developed while the disease was still in its early course." He suggests the term "signal symptom" for the transitory symptom which commonly occurs months or even years before the

patient recognizes the existence of an illness, and before the disease presents a recognizable syndrome. The commonest are minor disturbances of gait, visual disturbances, diplopia and "numbness."

R. M. Brickner (Arch. Neurol. and Psychiat. 36:586 (Sept.) 1936) describes a new symptom which he has named "*oscillopsia*." "It occurs commonly, but not exclusively, in patients with multiple sclerosis. The patient complains that objects seem to move back and forth, to jerk or to wiggle. The oscillation occurs only on walking or on fixation of gaze. A variant of the symptom is diplopia elicited by walking; the diplopia may occur concomitantly with or independently of the oscillating sensation." Oscillopsia seems to depend on the presence of nystagmus, intention tremor of the head or on a combination of these factors.

## THE MYOPATHIES

By ELI MARCOVITZ, M.D.

This group is still most obscure. The uncertainty concerning its make-up is reflected in the numerous classifications which have been proposed and are still being proposed. None of them are satisfactory. The reason lies in the numerous transition types of myopathy which are invariably encountered in any extensive experience with these cases. Among the true myopathies one includes: amyotonia congenita, pseudohypertrophic dystrophy, progressive muscular dystrophy, myotonia atrophica, myotonia congenita (Thomsen's disease), facioscapulo and facioscapulohumeral types, the distal type of dystrophy, and myasthenia gravis.

Much very suggestive work has been done recently on the chemistry of these disorders. This is still very much in the fact-gathering stage, but it will probably

result in real additions to knowledge of this problem. The work centers about the creatine-creatinine excretion in the various myopathies, and the chemical content of the muscles in these disorders, especially in relation to creatine phosphoric acid.

Because of failure of the muscle properly to utilize creatine, resulting in excessive excretion in some forms of myopathy, the **aminoacid glycine** has been fed to patients with varying results. This has been supplemented by **ephedrine** or **benzedrine** in some cases. The treatment has been rationally directed by the chemical studies, but is still not the answer to the problem. There is much that remains to be clarified concerning the fundamental nature of the disorder in the myopathies. For this, chemistry

must be looked to at least for a partial answer.

**Symptomatology.**—E. G. Zabriskie, C. C. Hare and M. M. Harris (Bull. Neurol. Inst. New York 5:526 (Aug.) 1936) observed a combination of 3 distinctive clinical signs in 5 cases of *progressive muscular dystrophy*. The triad consists of (1) contractures appearing very early in the course of the illness and involving the larger joints; (2) a pseudo-hypertrophy of the anterior tibial muscle group, with great loss in motor power; (3) a deformity of the mandible which exhibits a very wide angle, a malocclusion of the front teeth and a wide spacing of the lower front teeth.

**Treatment.**—A. Wolf (Arch. Neurol. and Psychiat. 36:382 (Aug.) 1936) reports 4 cases of *myotonia congenita* in which 10 grains (0.6 Gm.) of **quinine dihydrochloride** injected intravenously, abolished every myotonic phenomenon within 10 minutes, the effect lasting from 15 to 20 hours. Quinine hydrochloride, 5 to 10 grains (0.3 to 0.6 Gm.), by

mouth, 2 to 3 times daily, proved to be an adequate maintenance dose. Just how the drug acts in this disease is not clear. "Lindsley and Curran believe that the after-contraction of myotonia is of reflex origin, and is due to the persistent discharge of hyperexcitable sensory end-organs in muscle. In the light of their work, it seems that quinine is effective against myotonia through its diminution of reflex action." The author concludes that quinine is a specific for myotonia.

W. H. Everts (Bull. Neurol. Inst. New York 4:523 (Dec.) 1935) reports 2 cases of *myasthenia gravis* in which the patients were relieved of symptoms and restored to health by the oral administration of **prostigmine**, continued for a period of months. The dosage used was 30 mg. ( $\frac{1}{2}$  grain), 3 times daily. The author claims that the oral administration of prostigmine is safe, does not produce gastric or intestinal disturbance, can be continued for indefinite periods, and is a satisfactory method of therapy in *myasthenia gravis*.

## NARCOLEPSY

By ELI MARCOVITZ, M.D.

**Treatment.**—H. Ulrich, C. E. Trapp and B. Vidgoff (Ann. Int. Med. 9:1213 (Mar.) 1936) report 6 cases of narcolepsy treated with **benzedrine sulphate** by mouth. The dosage varied from 20 to 50 mg. ( $\frac{1}{3}$  to  $\frac{5}{6}$  grain) daily. All cases showed marked relief of symptoms. Inhalation was tried in 4 cases, with slight benefit in 1 case, moderate in 2, and no relief in the other case. Mild gastrointestinal symptoms, such as slight nausea or slight anorexia, may accompany the beginning of oral medication.

M. Prinzmetal and W. Bloomberg (J. A. M. A. 105:2051 (Dec. 21) 1935) also used **benzedrine** by mouth on 9 patients. These patients all fell asleep at

least 3 times a day. In 7 cases, cataplexy and other conditions associated with narcolepsy were present. Seven had been taking **ephedrine** for some time. Only 1 had been relieved, 5 were improved, and 1 showed no change. Under benzedrine treatment all 9 obtained complete relief from the attacks of sleep, and practically complete relief from cataplexy. The authors consider that benzedrine is about 3 times as effective as ephedrine. They recommend starting with a 10 mg. ( $\frac{1}{6}$  grain) dose daily, and gradually increasing the amount until the attacks are stopped. The highest dosage they found to be required was 40 mg. ( $\frac{2}{3}$  grain) 3 times a day.

## TRAUMA TO CENTRAL NERVOUS SYSTEM

By ELI MARCOWITZ, M.D.

**Sequelæ.**—E. J. Carroll, Jr. (Am. J. M. Sc. 191:706 (May) 1936) describes a composite picture of the state known as "*punch-drunk*." It occurs usually in the pugilist of the type known as a "fighter" rather than a "boxer." The "fighter" receives a great deal of punishment, and after a few years shows signs of "softening up." His tolerance to blows is reduced, and his timing begins to fail. Meanwhile, he develops some deterioration in attention, concentration and memory, and may become very sociable and voluble. An impediment in speech and a "glassy stare" may develop. These symptoms progress for a year or so and then usually become stationary. "Thus punch-drunk is a self-limited rather than a progressive encephalopathy." The more severe cases may develop marked thickness of voice, unsteady gait, difficulties in vision or hearing, and more severe mental and personality changes, with emotional instability. Involuntary habit movements of a boxing nature are common.

It is characteristic of this condition that there is no insight. "Punch-drunks almost universally do not realize that there is anything abnormal about themselves or their conduct, and will hotly resent, often with their fists, any application of this stigma to themselves." This is in sharp contrast to the usual postconcussion syndrome, in which subjective complaints are prominent and objective changes are not often seen.

The author discusses the possible anatomic changes occurring in the brain in this condition. He mentions the possibility of multiple punctate hemorrhages, and of tissue changes, such as hyperemia and edema following the blow, with consequent disturbances of nutrition. No pathological studies have been made.

A. Blau (Arch. Neurol. and Psychiat. 35:723 (Apr.) 1936) investigated the cases of 22 children who were at the Psychiatric Division of Bellevue Hospital with *mental changes following head trauma*. He classifies the conditions observed as posttraumatic acute psychosis, posttraumatic chronic behavior disorder, posttraumatic epilepsy with secondary deterioration, and posttraumatic defect conditions and secondary intellectual deterioration. Six children developed the *posttraumatic acute psychosis* and the onset occurred immediately after recovering consciousness. The symptomatology consisted of unrestrained instinctual, emotional and motor behavior, associated with an effect of fear and anxiety. Complete recovery occurred in a few weeks. In 12 children the *posttraumatic chronic behavior disorder* was observed, resembling closely the postencephalitic type. These children showed hyperkinetic, uninhibited, asocial behavior, with an instinctual coloring. Delinquency was present in all these cases. Intelligence was within normal range. General prognosis was poor, and many patients required prolonged treatment in hospitals for mental diseases. *Posttraumatic epilepsy* occurred in 5 children. It often led to behavior disorders and ultimate intellectual and emotional deterioration.

Blau believes that *mental deficiency* is a rare sequela of head trauma, although a form of secondary intellectual deterioration may occur as a result of a lack of interest and attention and of easy fatigability. Simple cerebral defect conditions, such as *aphasia* and *intellectual loss*, may occur as a result of head trauma. Blau suggests the posttraumatic organic behavior disorder in children may result from a localized lesion of the prefrontal association area of the brain.

## PSYCHIATRY

Edited by KENNETH E. APPEL, M.D.

## FEEBLEMINDEDNESS

By ROBERT A. MATTHEWS, B.S., M.D.

**ETIOLOGY.**—*Heredity.*—While the tendency in certain quarters has in recent years been away from the belief that heredity is all important as an etiological factor in feeble-mindedness (Berlin Correspondent: J. A. M. A. 106: 1675 (May 9) 1936), an investigation of nonheredity in a group of cases in Germany would indicate that only a small percentage of mental defectives should be so classified.

A study of the first 80 cases recorded in a genealogical table by the Department of Genetics of the Erfurt (Thuringia) Municipal Health Bureau shows 51 patients who have attended the school for backward children. It could be demonstrated that 76.47 per cent. of this group were afflicted with hereditary disease; an hereditary taint could not be proved in 6 cases, an exogenous injury was a factor in 2 cases, and neither exogenous nor endogenous injuries could be detected in 4 cases. On the basis of these observations, the relative incidence of hereditary and nonhereditary feeble-mindedness in early childhood was verified. The marked rarity of nonhereditary feeble-mindedness was likewise demonstrated. Since the first school years are the most propitious for such examinations and offer the best criteria, 72 pupils of the school for backward children were made to fill out a special questionnaire and examination blank. The gathering of accurate data was hampered, since occasionally the mother or father was unknown. Despite this handicap, 236 brothers and sisters were established. Of this number alone, 20.3 per cent. attend school for backward

children—in other words, are mentally deficient. In all, 47.2 per cent. of the 72 have tainted brothers and sisters, without including many borderline cases. Similarly, tainted parents, grandparents and so on, were discovered in 52.8 per cent. of the persons studied. This number is increased by about 4 when the entire tainted genealogy is considered. Therefore, 52 cases, or 58.33 per cent. of the total, present histories of hereditary taint. By careful computation, a maximum figure of 64 hereditary cases is arrived at against 8 nonhereditary cases, a proportion of 88.8 per cent. to 11.1 per cent.

E. Kleindienst (Monatschr. f. Kinderh. 64: 24 (Nov. 12) 1935) studied the *age of parents* and *order of birth* in connection with mental and physical defects of offspring. Investigations of 48 families that had a large number of children but were apparently free from hereditary defects revealed to Kleindienst that the fifth child is most often involved as regards physical defects. She points out that the mother is generally more than 30 years old at the birth of this child. In investigating the influences responsible for mental deficiencies, she observed that the first child is most often affected. This arouses the suspicion that the frequent impairment of the first born might be related to *birth injuries*. In evaluating the practical significance of these studies, the author states that the defectiveness of the first-born child does not necessarily indicate that the family should have no further offspring. If a defective child is born, the heredity should, of course, be carefully investigated; but, if hereditary defects can be

excluded, further offspring are not contraindicated unless the difference in the ages of the parents is extremely great or the mother is old or has been weakened by a rapid succession of births.

H. Luxenburger (Monatsschr. f. Kinderh. 65:109 (Mar. 4) 1936) challenges the conclusions reached by Kleindienst as regards the higher incidence of mental defects in *first-born children* as a statistical error. The author adds that his criticism of Kleindienst's conclusions does not apply to that author's observations regarding physical defects.

**Inbreeding.**—J. Manne (Ment. Hyg. 20:269 (Apr.) 1936) reports his investigation of mental deficiency in a closely inbred mountain clan in Virginia in which large families live in barely furnished one-room huts. Food is scarce and the diet poor; clothing and supplies are inadequate. Isolated, indifferent or hostile to strangers, with little interest in religion, recreation or culture, these people are ignorant of all that goes on outside their immediate world. Living under unhygienic conditions and lacking facilities for self-improvement, they are slowly undergoing racial disintegration.

Excessive childbearing, privations and work under primitive conditions make life especially hard for women. A study of individual persons shows, nevertheless, the development of sturdy characteristics of personality, in spite of the unfortunate circumstances. Sympathy for suffering, devotion and a sense of responsibility can command the respect and obedience of the group.

Study of infection with hookworm in this region indicates that it is a prominent cause of physical and mental disease; poorly-balanced, insufficient diet is another factor.

A careful analysis of inbreeding for several generations between members of a defective family, with many records of early death, feeble-mindedness, congenital disease, tuberculosis and cleft palate, revealed conditions that resulted in many instances in early death, illegitimacy, drunkenness, murder, cancer, mental disease and poverty. This suggests the necessity of acquainting the more intelligent members of the community with the seriousness of the problem.

## PSYCHOANALYSIS

By O. SPURGEON ENGLISH, M.D.

In a clinical study of euthanasia, Felix Deutsch (Psychoanalyt. Quart. 5:347 (July) 1936) states in the beginning that he would like to present a little picture book of the dying, "illustrations which certainly cannot be said to have a 'happy ending,' but nevertheless have an ending which does not leave us inconsolable."

Euthanasia, literally translated, means the art of dying easily and painlessly. The ancients had different words for describing the process which leads to death. When people speak of fearing death, they really mean that they fear the events

which lead to dying. In other words, it is the source of death which is feared rather than the condition of "being dead" in itself.

The author points out that "since life does not usually end 'normally,' but from disease, the threat of disease which results in dying and in death is a process upon which a mobilization of all the instinctual energies must ensue. Now every menace of the kind is felt as an aggression from without, as a threat of punishment. The aggression against the ego is felt and leads to a defensive reaction which may manifest itself against

the outside world, or conversely, in a masochistically pleasurable suffering. But the more the illness is regarded as an unavoidable danger, one from which there is no escape, one against which there is no possibility of defense, the more the ego feels that the game is up and the greater is the increase in the fear of death from which flight into psychosis is often the only way of escape.

"We see, then, that in order for death to be anything else than a torment, there must be a settlement of differences, a reconciliation among the operative forces of the aggressions, the anxiety, the sense of guilt, and the agencies from which they proceed. Nevertheless before these instinctual forces come to terms with one another, each of them seeks to justify itself by an increase in intensity or by achieving satisfaction."

The author cites a case of angina pectoris in which the fear of death was very great. He was accustomed to speak of his paroxysms as follows: "Now the devil is loose once more in my chest; he has me again in his clutches." Psychological investigation showed the devil in question signified his mother, against whom he had considerable hatred. In discussions of her, whom he hatefully loved, his paroxysms were most intense as a result of recalling threats of punishment reminiscently charged with anxiety. In spite of being nearly 60 years of age at the time of psychological treatment, he is still, after 8 years, free of pain and anxiety and reconciled to the approach of death as a result of resolution of his ambivalent emotions.

The dread of parturition, from which many women suffer, may be intensified into a fear of death. Especially is this true when the mother has been hated and death wishes have been felt against her. The fear expressed runs as follows: "I know I shall die in childbirth—as I wished my mother would die."

One case with such a conflict after normal delivery under the most aseptic precautions developed unexplained fever and delirium in which the dread of death found sinister expression two days later. Another female patient, gravely injured and who knew that the possibility of death was very likely, became obsessed with vivid memories of her mother. Her constant thought was "Now, Mother, you have me where you wanted to have me." This left her peaceful and free from anxiety.

The author comments that freedom from anxiety while dying may be a masochistically pleasurable experience. "Dying, however, means not only that one must desert the object of one's love, but must also be deserted by that object. This loss of object arouses dread and anxiety if no substitute can be found. To avert this anxiety many of the moribund free themselves from the ambivalence of their attitude toward their 'nearest and dearest,' clinging to them and dying peacefully only when all are assembled around them." Instead of a clinging to object relationships there may, conversely, be an abandonment of them, as shown by certain seriously ill individuals who become greatly annoyed with friends, relatives, or physician when death is impending and will have nothing to do with them.

From the literature, the author draws the case of a man who could die peacefully only after he had expressed himself in a tirade against a rival, and of another who, being the victor, detached himself from earthly object-relationships and put his trust in a world beyond, a plane above his earthly judges.

Another psychological mechanism that makes dying easier is a state in which the patient imagines himself in contact with someone previously loved. Some person near, either husband, wife, or other relative, is misidentified and called

by the name of the earlier loved one. Belief in being united with this earlier object, which is often brother or sister, results in a peaceful and happy death.

In conclusion, the author says: "Under what condition does euthanasia occur? The answer may be given as follows: Euthanasia occurs when all aggressive reactions subside, when the fear of death has been dispelled and when there is no question of a sense of guilt. What makes

such happiness in dying possible? It would seem that it is the fact that the path of regression of the libido to the objects of infantile love, apparently associated early in childhood with an intense sense of guilt, can be retrodden without any sense of guilt. Before freedom from a sense of guilt can be achieved, however, guilt must be atoned for by the knowledge of imminent death with all its physical consequences."

## PSYCHONEUROSES

By J. BRACELAND, M.D. and D. W. HASTINGS, M.D.

**TREATMENT.**—P. Solomon and M. Prinzmetal (Boston Soc. Psychiat. and Neurol. (Mar.) 1936) report that **benzedrine sulphate** is a valuable adjunct to hyoscine and stramonium in the treatment of *post-encephalitic parkinsonism*. R. A. Matthews used benzedrine in conjunction with stramonium, hyoscine and atropine and reports that 75 per cent. of his patients showed definite improvement, which he attributed to the benzedrine alone, since no change was made in the medical régime previously employed. The dosage used varied between 15 and 90 mg. ( $\frac{1}{4}$  and  $1\frac{1}{2}$  grains) of the drug daily.

S. A. Peoples and E. Guttman (Lancet. 1:1107 (May 16) 1936) have shown that benzedrine has a good effect upon some *depressed moods* and they noticed an increased talkativeness and a tendency to euphoria. Retardation was lessened and improvement was noticed in the patients' movements. The effect of the drug on mood and fatigue in normal and neurotic persons was studied by A. Myerson (Arch. Neurol. and Psychiat. 36:816 (Oct.) 1936). He found that nonpsychotic and nonneurotic individuals who suffer from *fatigue* due to lack of sleep receive quick relief (often of a pleasant type) by taking 5 to 20 mg. ( $\frac{1}{12}$  to  $\frac{1}{3}$  grain) of benzedrine on aris-

ing. If the drug is taken late in the day, the sleep mechanism is disturbed and sleep is often impossible.

Benzedrine has been used by R. A. Matthews in small doses on psychoneurotic patients with *fatigability* and *morning depression* and finds it a useful therapeutic agent. A. Myerson, J. Loman and W. Dameshek (Am. J. M. Sc. 192:560 (Oct.) 1936), in studying its physiological effects, finds that benzedrine has a striking and prolonged effect in raising blood-pressure and causes a concentration of blood constituents by reason of its vasoconstricting action. Basal metabolism and blood sugar readings were not affected. When used as an antagonist to sodium amytal, it did not lessen the depth of narcosis but shortened its duration and tended to overcome the fall in blood-pressure produced by the barbiturate. Thus, it might find a place as an antidote in *poisoning by barbiturates*.

F. J. Braceland and D. W. Hastings had occasion to use benzedrine in a case of *attempted suicide with morphine* and observed that the patient was benefited. H. Ulrich, C. E. Trapp and B. Vidgoff (Ann. Int. Med. 9:1213 (Mar.) 1936) report that the drug is of greater value than ephedrine in the treatment of *narcolepsy*.

## ORGANIC PSYCHOSES

By CLIFFORD B. FARR, M.D.

**Psychic Manifestations of General Disease.**—A case of *Schilder's disease* is discussed by A. Meyer and F. Pilkington (J. Ment. Sc. 82:812 (Nov.) 1936) which showed diffuse demyelination together with circumscribed lesions resembling patches of disseminated sclerosis. They feel that this case offers support to the theory that all the demyelinating diseases are pathogenically related and that the diffuse types may be the consequence of coalescence of disseminated lesions. Their studies also suggest that these diseases spread through the blood vessels (veins) rather than from the spinal fluid.

Another large group of articles deals with the technic and therapeutic results of *hyperthermia in paresis*. The weight of opinion still seems to favor the malaria technic for all except special cases, in contrast to hyperpyrexia induced by physical means. As regards the latter, heated air, circulated by electrical blowers, is tending to be used in place of diathermy. F. G. Ebaugh (Am. J. Psychiat. 93:191 (July) 1936) calls attention to delirious episodes frequently associated with artificial fever therapy; 331 delirious episodes occurred in 1324 fever sessions, but only 9 of these episodes were severe enough to be classified by psychiatrists as "true" or classical delirium. Malaria induced by the bite of infected mosquitoes (E. Kusch, D. F. Milam, W. K. Stratman-Thomas: *Ibid.* 93:619 (Nov.) 1936) seems to offer special advantages, both as to therapeutic efficacy, freedom from severe or atypical reactions, and the avoidance of any danger of conveying syphilis in cases of uncertain or mistaken diagnosis. It is not practical for every-day use, because the infected mosquitoes are only available in hospitals with a special

technical staff. From a statistical standpoint, all these forms of treatment give favorable results which are roughly comparable. Formerly, paretics never, or rarely, recovered and on the average lived 3 to 5 years. "By modern methods of treatment more than half of the paretics admitted are out of the hospital in 3 years and the majority of these in less than 6 months" (C. W. Hutchings: *Psychiatric Quart.* 10:99 (Jan.) 1936).

C. H. Frazier (Arch. Neurol. and Psychiat. 35:525 (Mar.) 1936) tabulated the incidence of various mental phenomena in 105 verified cases of frontal lobe tumor: Loss of memory, 41; loss of intelligence, 34; loss of attention or inability to concentrate, 28; change of personality, 24; disorientation, 17; emotionalism, 12; crying, 4; irritability, 10; Witzelsucht (making light of everything), 3; euphoria, 6; childishness, 6; hallucinations, 6; indifference, 5; profanity, 2; apraxia, 1; aphasia, 7. One or more symptoms characteristic of mental disturbance were recorded in 60 of the 105 cases in this series. Frazier points out that *mental disturbances are one of the earliest signs of tumor in the frontal lobe*, and while not pathognomonic, have localizing value. Loss of memory is chiefly for recent events. Impairment of intellectual ability is shown by poor judgment and mistakes pertaining to business. Change in personality includes, in addition to the more obvious items usually enumerated, some insidious feature that is apparent to the family, but not easily described. Schwab calls this "flavor," and specifies the impression made by the patient as pleasing, disagreeable, revolting, suspicious or charming.

M. Kreschner, M. B. Bender, and I. Strauss (*Ibid.* 35:572 (Mar.) 1936)



found no difference in the frequency of mental symptoms between tumors of the frontal (64 cases previously reported by them) and temporal lobes, respectively. They, therefore, discount the localizing value of mental symptoms in frontal lobe disease. Except for the *greater incidence of complex hallucinations, dreamy states and uncinate phenomena in the cases of tumor involving the temporal lobe*, there was no significant difference in frequency and nature between the mental symptoms of the temporal lobe and those of tumor of the frontal lobe. In a subsequent review of 120 cases of subtentorial tumor (*Ibid.* 37:1 (Jan.) 1937), mental symptoms were observed in 56 (47 per cent.), were early manifestations in 14 patients (12 per cent.), and the first symptom in 3 patients (2½ per cent.). Mental symptoms in cases of subtentorial tumor were much milder and less complex than those in cases of supratentorial tumors. In explanation of the great variation in the incidence of mental symptoms reported in brain tumor, Kreschner and his associates remark that it depends in part on who examines the patient and whether special attention is paid as to whether the patient presents abnormal mental states.

I. N. Wolfson (*Psychiatric Quart.* 10:5 (Jan.) 1936) has reviewed the literature with reference to mental symptoms and brain tumor and reports 2 personal cases in which they were the most prominent and, in 1 case, practically the only focal manifestation. Incidentally, he states that Kinnier Wilson believes that the localizing value of mental symptoms in cases of cerebral tumors is practically nil. He (Wilson) looks upon the likelihood of the occurrence of mental symptoms as dependent upon the relationship of the tumor to the two chief associational systems of the cerebrum, *i. e.*, the corpus callosum and the inferior longitudinal fasciculus. This sub-

ject is too complex and the theories too various to make further detailed discussion profitable. Brander is quoted as saying that the tumor merely determines the onset of what was a latent characteristic in the individual.

B. J. Alpers (*J. Nerv. and Ment. Dis.* 84:621, 1936), on the basis of recent observations, defines the mental syndrome which is characteristic of the involvement of the corpus callosum somewhat more specifically than hitherto. He says that the *mental symptoms in callosal tumors* are characterized first and foremost by inability to concentrate, difficulty in thinking, and, above all, as shown in both his recent cases, by what may be called complete imperviousness to stimuli of all sorts, particularly auditory. This is not due to an aphasic difficulty, but results partly from lack of attention and partly from blocking. Hence, the response to questions is irrelevant. The changes in personality and psychotic episodes which have been described in callosal tumors are merely incidental. They result probably from invasion of the frontal lobes and from the increased intracranial pressure.

D. W. Hastings (*Weekly Roster and Med. Digest.* 31:1206, 1936), studying 25 cases of undiagnosed *brain tumor* in patients over 40, found 5 which were characterized by psychic changes and a terminal sudden development of paralysis. The mental picture was one of gradual loss of concentration and higher intellectual faculties associated with thick speech, confusion and character change. While in the hospital, all these patients developed hemiplegia and died within a very short period. In all (25) cases, the 3 cardinal symptoms of brain tumor were absent.

The modification of *behavior* consequent upon *cerebral lesions* is discussed by K. Goldstein (*Psychiatric Quart.* 10:586 (Oct.) 1936). This article covers:

a wider field than brain tumors, but is worthy of a brief citation. In this connection, he says that the characteristic difference between the older and the more recent orientation in psychopathology is, it may be said, that the former tends to regard the individual symptoms or the individual syndromes by themselves, while the more recent point of view regards every single phenomenon as an expression of the struggle of the personality changed by disease with the task confronting it. From this angle, the problem of the total behavior of the patient suffering from brain lesions acquires a special significance. He especially emphasizes the influence of "catastrophic situations" in their relation to the total behavior of the patient under given conditions.

An indirect light on the symptoms of cerebral lesions is afforded by an interesting case of *prefrontal lobe extirpation* reported by S. Ackerly (Am. J. Psychiat. 92:717 (Nov.) 1935). In the patient reported, possibly three-fourths of all prefrontal lobe tissue was destroyed in removing a tumor in three stages. After the first stage, the individual was apathetic, dull and showed memory impairment: after the second stage, she was brighter but disoriented, hallucinated and irritable (irritation phenomena); but after the third stage, all these bizarre manifestations cleared up at once and she was left in normal contact with her past as well as present, and with a feeling of well-being and an emotional exaltation. At the expiration of 2 years she is normally responsive to anything at hand, appears little concerned with anything remote. Her persistency and perseverance seemed to be somewhat dependent on this lack of distractability. Increased capacity to work without fatigue, increased sex urges, diminished anxiety with free emotional expression in general can, the writer believes, be

conceived as a loosely-knit syndrome. Her energy tends toward "quantity" production rather than "quality," though she is capable of the latter. The patient rates as well as the average American by both intelligence and performance tests.

In recent articles White and Kennedy express more or less divergent tendencies in present-day psychiatry. W. A. White (Ment. Hyg. 20:189 (Apr.) 1936) emphasizes the concept of the organism as a whole, implying a recognition not only of the continuity of life, but that all the steps in the development are related. This, he believes, is true not only in the physical development, but in the physiological as well. The concept of the unconscious leads to the belief that back of what happens to be the focus of the attention, lies millions of years of life which expresses itself at the psychological level of development as tendencies, drives, wishes, instincts. Mental and physical symptoms come to be recognized not as parts, but as relations and aspects of an organism which functions as a whole. F. Kennedy (New England J. Med. 214:1095 (May 28) 1936) on his part, recognizes that Freud has demonstrated that there is a phylogeny of personality, but feels that psychoanalysis is one angle of view only. He stresses the progress that has been made in the study of diseases of the mind by the methods of neurology and general medicine and makes a plea for continued research along these lines.

G. W. Thomas (Am. J. Psychiat. 93:693 (Nov.) 1936) studied the relation of *psychic factors to rheumatoid arthritis*. He reminds us that the condition has been attributed to emotional shock at least since the VII century A. D., and that this relationship has been emphasized recently by Millard Smith (1932). Thomas also believes that a group of prodromal and concurrent symptoms,

chiefly vasomotor and gastrointestinal, are readily recognized as often due to emotional disturbances. To determine how frequent the occurrence of serious emotional disturbance is observed before the frank onset of the disease, he studied 31 patients, without special selection (except as to ability to understand English). He found in *all* a "fairly severe" emotional disturbance of one kind or another, which had been present before any sign of arthritis. Many of these traumas were of a frankly sexual nature; others included hysteria of various types, obsessional neuroses, gastrointestinal disturbances, etc.

H. A. Nissen and K. A. Spencer (New England J. Med. 214: 576 (Mar. 19) 1936) found psychiatric and endocrine disturbances in 22 per cent. of 500 cases of *arthritis* which they reviewed. In this group, psychogenic and endocrine disturbance had been dominant before and during the early stages of arthritis. He noted a striking similarity between a group of schizophrenic and arthritic patients. The object of each is to escape reality. The schizophrenic achieves this by the mechanism of phantasy or dream state in its variations; the arthritic, by somatic or physical pathways through functional disability.

## SCHIZOPHRENIA

By F. J. BRACELAND, M.D., and D.W. HASTINGS, M.D.

**Treatment by Insulin Shock Therapy.**—One of the most important lines of psychiatric investigation to be brought to light in recent years is the introduction of insulin shock therapy in the treatment of schizophrenia by M. Sakel (Deutsche. med. Wchnschr. 56: 1777 (Oct. 17) 1930; "Neue Behandlungen der Schizophrenie," Vienna, M. Perels, 1935). Quite by accident, he observed a change in the mental status of some patients who, while under insulin treatment for morphine addiction, inadvertently went into shock. He then began to work with psychotic patients and as he says, "It was at this time that insulin treatment was changed to hypoglycemic shock therapy." The work was initiated in 1928, but he did not begin to publish it until 1933. In the interim he had noted some rather marked results and was encouraged to go on. New disciples appeared, notably Müller, of Bern, Switzerland, who also reported favorably on the therapy, particularly in cases of schizophrenia which heretofore had been considered hopeless.

The work soon gained favor in this country and was accelerated by the reports of B. Glueck (New York State J. Med. 36: 1473 (Oct. 15) 1936), J. Wortis (J. Nerv. and Ment. Dis. 84: 497 (Nov.) 1936), and the group at Worcester State Hospital under the direction of Hoskins.

Sakel himself was invited to America to lecture and discuss his treatment, and gave a six-weeks' course of instruction to physicians of New York State at the Harlem Valley State Hospital.

Sakel and others who are working with this therapy make no claims, but simply state their observations conducted over varying periods of time and chronicle their results. There is little or nothing known of the actual physiology underlying the treatment; thus far the results are entirely empirical.

Peculiarly enough, the paranoid type of schizophrenia, which has heretofore been considered to have the gravest prognosis, apparently responds most favorably to the shock therapy. Catatonics, who had usually been regarded

as the most favorable from a prognostic angle, have not fared so well.

Most observers agree that the most favorable candidates for this treatment are those patients who have been ill less than a year and a half, and preferably less than 6 months; Sakel even goes so far as to state that he believes the recovery rate in the latter group approximates 80 per cent.

The therapy is divided into 4 phases:

1. *Introductory Phase*.—The patient is gradually given a dose of **insulin** sufficiently large to produce coma. The dosage usually starts at 20 units and is advanced 10 units daily until the "coma dose" is reached. Some patients need as little as 20 units, others as high as 300 units or over to produce coma. When the "coma dose" is established, the patient is then in phase 2.

2. *Shock Phase*.—The patient is daily put into insulin shock with the exception of Sunday. The shock or coma is permitted for 30 to 60 minutes on the average. It is generally found that once the coma dose has been reached, that dosage may be gradually reduced (often by one-third) and still produce coma or shock. Phase 2 lasts 6 to 8 weeks in the usual case.

3. *Rest Phase*.—This is merely the Sunday day of rest and runs concomitantly through the other phases.

4. *Transition Phase*.—After the shock phase has continued long enough (in the opinion of the physician in charge), the patient is gradually weaned from insulin by a daily reduction of the dose. This reduction is done generally in about 5 or 6 days.

The clinical improvement in the disease develops during the shock phase.

In the presence of such large doses of insulin, attention must be paid to the **diet**. The shock is interrupted by intravenous **glucose** or **sugar solution** by **stomach tube**. Sufficient **carbohydrate**

must be given to cover the amount of insulin administered. It will be remembered that 1 unit of insulin requires 2 grams of carbohydrate, and the diet is calculated accordingly. Various refinements in the original dietary régime are being made.

The possibility of *catastrophe* should be constantly borne in mind. *Convulsions* are the most alarming and dangerous of the symptoms noted. "*After-shock*," i. e., a recurrence of hypoglycemic symptoms, several hours after cessation of the daily treatment, is another danger.

There have been 4 fatal cases reported, several from "after-shock" and 1 from *acute hemorrhagic pancreatitis*.

A physician must be in constant attendance during the hours of treatment. Nurses are arranged so that one nurse watches only 2 patients. Therapy is best carried out in a separate section of the hospital, which is kept quiet and darkened, the better to facilitate coma.

Except for scattered reports concerning small groups of patients, no statistics are available except those of Sakel, as previously mentioned. The consensus of opinion is that the results are gratifying. It is too early to set forth lavish claims. One thing, however, is certain, and that is that the treatment is aimed at an illness which has heretofore proven to be most resistive to any form of therapy. The mere fact that it has helped even a small number of schizophrenics makes it imperative that it be investigated carefully and the results painstakingly tabulated.

[EDITORIAL COMMENT.—The Committee on Public Education of the American Psychiatric Association has considered it worth while to issue a public statement on the present status of the use of insulin shock treatment for schizophrenia. The following statement is made with the approval of all of the members of the Committee and also of the President

of the American Psychiatric Association. C. Macfie Campbell, professor of psychiatry in Harvard University (*J. A. M. A.* 108:560 (Feb. 13) 1937): "The impression that there never has been and is now," says the statement, "no treatment for dementia precox, except through insulin therapy, is entirely erroneous. While dementia precox has a less favorable outlook than many other forms of mental illness, much has been done and there are many forms of therapy each promising something. It is hoped, and may prove to be a fact, that the so-called insulin shock treatment for dementia precox will find a useful place among the forms of treatment for dementia precox, but its exact value has yet to be determined and it can be definitely stated that it is not a specific, nor by any means a cure for all cases of dementia precox. It would be a source of regret should the insulin shock treatment be a means of holding out a false hope to the families of the tens of thousands of sufferers from dementia precox when this hope most certainly cannot be widely realized with present day knowledge of insulin therapy. It is, however, at the present time receiving careful study in the New York and Massachusetts State Hospital systems, Bellevue Hospital, New York, and other scientific centers, but it should not be undertaken except by those adequately trained to meet the dangers connected with the treatment."

In an Editorial (*J. A. M. A.* 107:1720 (Nov. 21) 1936), the work of Wilson is discussed. Present opinion in-

dicates that this treatment should be employed primarily in the early cases, although cases of long duration sometimes show satisfactory results. The treatment consists in giving the patient a series of doses of insulin, as a result of which he falls into a state of hypoglycemia. The injections are continued at frequent intervals until the desired result is obtained. As a rule, the first dose is from 15 to 30 units of insulin intramuscularly, given at 7 A. M., without previous food. The amount is increased by 5 to 10 units daily until a dose is reached to which the patient reacts with what is known as "insulin shock." The most important symptoms of satisfactory shock are sweating, hunger, bradycardia, epileptiform attacks, low temperature, salivation, mental changes and coma. If it is desired to stop the shock before the patient has gone into coma, from 150 to 200 grams of dextrose in tea or water may be given. Dextrose may be administered also by nasal tube or by intravenous route. The degree of response to treatment cannot be prophesied on clinical grounds.

Survey of the various theoretical explanations advanced for the success of this treatment reveals no solid ground of physiologic or pathologic proof, and the real mechanism underlying the symptoms and changes that have been observed remains unknown. Wilson points out that the treatment is neither too dangerous nor too unpleasant to exclude it as a means of treating the serious disorder known as schizophrenia.]

## OPHTHALMOLOGY

By CONRAD BERENS, M.D., and JOSHUA ZUCKERMAN, B.S., M.D.

**CHOROID.—SYMPATHETIC OPHTHALMIA.**—It is pointed out by A. C. Woods (Am. J. Ophth. 19:100 (Feb.) 1936) that in sympathetic ophthalmia the exciting and the sympathizing eyes present exactly the same underlying histological picture.

Sympathetic ophthalmia is characterized by infiltration of the uveal tract, particularly of the choroid, with round cells, epithelioid cells, and giant cells.

A characteristic change in the pigment epithelium is the formation of nodules of proliferating pigment epithelium with pigment phagocytosis, known as Dalen-Fuchs nodules.

Blood changes are not diagnostic nor prognostic in this condition.

**Treatment.**—With regard to treatment, Woods (*Ibid.*) points out that (1) **early enucleation** of the injured eye is a proved preventive measure, but is not an absolute guarantee against the development of sympathetic ophthalmia. It may develop from 2 weeks to 2 months after enucleation. Enucleation within a period of 2 weeks after injury is almost a certain preventive measure against sympathetic ophthalmia. (2) Maximum dilatation of the pupil is extremely important to prevent occlusion of the pupil. (3) **Sodium salicylate** as advocated by H. Gifford (1 grain—0.06 Gm.—per pound of body weight daily in divided doses, with **sodium bicarbonate**) is valuable. (4) **Non-specific protein therapy** is recommended, particularly **diphtheria antitoxin**. Twenty thousand units is given intramuscularly at daily intervals for a period of 1 week and if the ocular con-

gestion subsides, it is continued at weekly intervals for several weeks. If the congestion does not subside, the daily injections are continued until improvement results or symptoms of anaphylactic reaction develop; then they are given at weekly intervals in divided doses. (5) **Desensitization with uveal pigment** has been used with some satisfactory results.

Heat locally is of little value. The *prognosis* is favorable in 66 per cent. of the cases when treatment is begun in the early stages of the disease.

B. Samuels (Arch. Ophth. 15:59 (Jan.) 1936) recommends **enucleation** rather than evisceration in sympathetic ophthalmia, in order to remove extensions which may have taken place into the emissary vessels in the sclera. If the intraocular tension is high, repeated **paracentesis** should be performed beyond the limbus, because the cornea is the only structure which is free from inflammation.

**COLOR VISION.**—Zuckerman believes that the following data will assist in distinguishing between acquired and congenital color blindness:

In *acquired* color blindness: (1) Trauma or disease of the retina, optic nerve, or visual pathways is usually present. (2) The patient has noticed that his vision for color has failed. (3) Impairment of central and peripheral vision and of the light sense are usually present. (4) Only one eye may be affected. (5) Color vision may be absent only centrally (central scotoma) while present peripherally.

*Congenital* color blindness may be diagnosed qualitatively by the following tests: (1) Nagel's colored cards. (2) Ishihara. (3) Thomson's lantern. (4) Nagel's anomaloscope. (5) Ferree and Rand acuity lantern.

Color blindness may be measured quantitatively by: (1) Determining the smallest visual angle at which the color of an object may be recognized. (2) Determining the color threshold and minimum difference of distinction of colors. (3) Wolffberg's diagnostic color apparatus.

There is no *treatment* for color blindness, but **spectacles** in which **red-free filter glass** is attached to the upper part of the spectacle lens may be tried. A red traffic light when viewed through the red-free segment will appear black.

**CONJUNCTIVA.—PARINAUD'S CONJUNCTIVITIS.**—In a report of 2 cases, H. D. Lamb (Am. J. Ophth. 19:571 (July) 1936) found that histologic changes, including the presence of leptothrix, support Verhoeff's conclusions concerning the histopathology, which are as follows: Parinaud's conjunctivitis consists of a focal area of necrosis, 0.3 mm., or larger, beneath the epithelium on the surface. This is packed with endothelial leukocytes, containing broken-down chromatin granules. Eosinophilia of 4 per cent. was found in both cases. A solution of **silver nitrate** from 0.25 per cent. to 1 per cent., **copper sulphate stick**, **holocaine** and **hyoscine ointment** have been used locally.

**PLASMOMA.**—Four cases of plasmoma of the conjunctiva are reported by J. Pallarés Lluésma (Arch. de oftal. hispano.-am. 36:61 (Feb.) 1936) in patients with trachoma. Microscopic study of excised conjunctiva revealed plasma cells and connective and hyaline tissue. He recommends **excision**, **scari-**

**fication of the granules** followed by the instillation of solutions of **cyanide of mercury** (1:500 to 1:1000) and of **copper sulphate**.

**TRACHOMA.—Etiology.**—R. W. Harrison and L. A. Julianelle (Am. J. Ophth. 19:118 (Feb.) 1936) investigated the bacterial flora in 243 cases of uncomplicated trachoma, the bacteria from diseased eyes which had a similar clinical appearance, and from normal eyes. No typical bacteria were found and the same bacteria were also isolated from the normal eyes. They conclude that the bacteria cultivable from trachoma do not induce experimental trachoma in monkeys.

P. Thygeson (*Ibid.* 19:649 (Aug.) 1936) concludes that trachoma is a specific communicable disease not caused by a specific bacterium nor by repeated infection with ordinary conjunctival bacteria, but by a filtrable virus. This virus is probably relatively large and may be identical with the elementary bodies of Prowazek and Halberstaedter.

**Treatment.**—L. L. Krakhmalnikov (Sovet. vestnik oftal. 8:106, 1936) reports that the follicles are destroyed and the infiltration in the conjunctiva and tarsus is diminished in the acute stages of trachoma by repeated **massage** and **expression of the follicles** with a Desmarres lid elevator. Expression should be repeated every 10 to 15 days.

A. F. Lenzen and H. S. Gradle (Am. J. Ophth. 19:665 (Aug.) 1936) report that only 54 of 900 cases of trachoma resisted treatment **massage** with **chaalmoogra oil** and a solution of **oxycyanide of mercury** 1:5000 together with **surgical correction of complications** from 4 to 12 months of active treatment were usually required to bring about a quiescent stage. Relative freedom from scarring and complications justified the additional time required.

Acute symptoms subsided in 2 weeks in 38 of the resistant cases after treatment with quinine bisulphate. The treatment was continued for from 2 to 12 months. Treatment with quinine bisulphate is recommended because it is efficacious and results in only slight scarring and few complications.

From results obtained in the treatment of trachoma with subconjunctival injections of **trachocid (bee virus)**, A. Lobel (Klin. Monatsbl. f. Augenh. 96: 374 (Mar.) 1936) concludes that this virus is reliable, efficient, nonirritating, and painless. In his series of 11 cases complicated by involvement of the cornea, about 10 or 15 injections were adequate.

### CORNEA, DISEASES OF.—

**Treatment.**—Good results by the local use of quinine in some diseases of the conjunctiva and cornea are reported by E. Selinger (Arch. Ophth. 15: 31 (Jan.) 1936). Quinine is bactericidal, astringent, and mildly anesthetic. A 10 per cent. aqueous solution or 2 or 4 per cent. ointment is effective in old *corneal opacities*, *trachoma*, *interstitial* and *disciform keratitis*.

**KAYSER-FLEISCHER RING IN WILSON'S DISEASE.**—Four cases of the Kayser-Fleischer ring in Wilson's disease, one of which was associated with microcephaly, are reported by L. Bothman and D. E. Rolf (Am. J. Ophth. 19: 26 (Jan.) 1936). Three were cases of Wilson's disease, although enlargement of the liver and impaired liver function were absent. The fourth was associated with microcephalus in a girl 8 years of age whose brother's case is included in this group of cases. They point out that not only has the Kayser-Fleischer ring never been observed in such a young patient, but that it has never been reported associated with microcephalus.

The Kayser-Fleischer ring consists of a band or a brownish-green ring of pigment from 1 to 2 mm. wide. The pigment lies in Descemet's membrane adjoining the limbus. The condition is bilateral.

The *symptoms* of Wilson's disease are as follows: rhythmic tremor of the extremities, body and head, hypertonia with hardness and rigidity of the muscles, contractures of the extremities (which may simulate bilateral hemiplegia), difficulty in articulation and swallowing, drooling of saliva, anorexia, atrophy, emaciation, psychic or mental changes with dementia, and the absence of pupillary anomalies, ocular palsies, or nystagmus.

The disease ends fatally in from 2 to 4 years. Treatment is useless.

In the classical type of Wilson's disease the liver is involved.

**KERATITIS.—Etiology.**—During a period of 2 years D. Rankine (Brit. M. J. 2: 6 (July 4) 1936) observed 1598 cases of keratitis produced by *artificial silk*. The symptoms consist of blurring of vision, halos, a sensation of grittiness, photophobia, lacrimation, blepharospasm, dull aching at the back of the eyes, and headache. More severe cases presented superficial desquamation of the corneal epithelium and circumcorneal injection; the breath was suggestive of onions. The onset of the attack frequently occurred not immediately after exposure but on the next day. *Treatment* consisted in removing the patient from the spinning room or acid house to quarters with better ventilation. **Cocaine** (0.5 per cent.) in **zinc ointment** was used locally. Two 8-hour exposures were usually necessary to produce symptoms. Some cases were due to *thioformaldehyde* which is produced at one stage in the process of manufacture.

A. Magitot, H. Tillé and Dubois-Poulsen (Ann. d'ocul. 173: 1 (Jan.)



1936) state that intranasal disease may produce keratitis either by serving as a focus of infection, or by producing trophic disturbances of the cornea from irritation of the nasal nerve by intranasal pathologic conditions. After **cocainization** or **cauterization of the inferior turbinate**, improvement of the corneal condition often results. Some types of follicular conjunctivitis respond to treatment of intranasal disease.

**Treatment.**—J. Green (Am. J. Ophth. 19:16 (Jan.) 1936) agrees with the views of Ewing and Allen that the cause of *bullous keratitis* is disease or alteration of Bowman's membrane. He **excised Bowman's membrane** in 2 cases. As a result of this procedure the newly-formed epithelium became adherent to the substantia propria.

A. Linksz (Klin. Monatsbl. f. Augenh. 96:233 (Feb.) 1936) describes a new method for the treatment of *parenchymatous keratitis resulting from congenital syphilis*. In 7 cases he obtained rapid and practically perfect clearing of the opaque cornea by **Schiek's intraocular autohemotherapy**.

F. Stocker (Schweiz. med. Wchnschr. 66:335 (Apr. 4) 1936) reports that he obtained cures in 3 cases of *superficial punctate keratitis* by administration of **vitamin A**.

**MEGALOCORNEA.**—M. U. Troncoso and I. E. Givner (Am. J. Ophth. 19:549 (July) 1936) point out that megalocornea, a hereditary disease of adults, is bilateral, and presents enlarged cornea, deep anterior chamber, iridodesis, and a tendency to the formation of cataract. They found that only the cornea and scleral limbus were involved in the apparent overgrowth; the other parts of the eye were only stretched to conform with this overgrowth.

**CORNEA PLANA.**—Cornea plana is a condition in which the radius of curvature of the cornea is the same as

that of the eyeball. H. Barkan and W. E. Borley (Am. J. Ophth. 19:307 (Apr.) 1936) report 3 cases in 1 family. An indistinct corneal opacity which extended from the limbus into the corneal tissue (described by Wilber Swett) was present in 2 cases. They believe that cornea plana is a hereditary and familial developmental anomaly of the anterior mesodermal segment of the eyeball. In cornea plana the anterior bulbus and cornea are flat and the angle at the junction of the cornea and sclera is absent. Embryotoxon (arcus juvenilis) is usually present. Cornea plana is considered a dominant, inheritable characteristic.

**CORNEAL ULCER, SERPIGENOUS.**—**Treatment.**—W. Grüter (Klin. Monatsbl. f. Augenh. 95:605 (Nov.) 1935) concludes from his experiences in the treatment of serpigenuous ulcer and ocular herpes that **short-wave radiation** is superior to diathermy. Heating of the tissues inhibits the growth of bacteria and increases local metabolic changes.

H. Schmelzer (München. med. Wchnschr. 82:1906 (Nov. 29) 1935) expresses the opinion that in the initial stages of serpigenuous ulcer, cauterization is contraindicated. **Optochin** or a solution of **zinc sulphate** or **tincture of iodine** should be applied to the ulcer. **Electrocoagulation** is indicated in the advanced stages.

**EYE.—DIAGNOSTIC METHODS.**—**Miotics.**—M. Wilenkin (Klin. Monatsbl. f. Augenh. 96:84 (Jan.) 1936) advocates the use of a new miotic, *doryl*, for cases in which pilocarpine is not tolerated or is no longer effective. In 28 cases (19 *glaucomatous* and 9 normal persons) 5 drops of doryl were instilled within 5 minutes in one eye (the fellow eye serving as a control). Examination showed that the intraocular tension decreased for 1 hour and then

rose, resembling the action of pilocarpine. Maximal miosis lasted 6 hours in 8 cases, and at least 20 minutes in every case.

**Ophthalmology in Neurological Diagnosis.**—E. Hartmann has studied chronic arachnoiditis of the cisterna chiasmatis. Arachnoiditis is a serous meningitis associated with a rapid or slowly developing increase in intracranial pressure. Symptoms suggestive of suprasellar tumor are simulated when arachnoiditis develops in the cisterna chiasmatis, around the chiasm and the intracranial portion of the optic nerve. History often reveals chronic infection of the nose and pharynx, cranial trauma or syphilis. The field defects in arachnoiditis seldom present definite bitemporal hemianopsia. The fields are more regular and occasionally present binasal defects and usually large central scotomas. Although the postoperative visual result is improved in only 50 per cent. of cases, **surgical intervention** followed by **x-ray therapy** and intravenous injections of **sodium iodide** for a period of several years is advisable.

**Traumatic Subdural Hemorrhage.**—Hartmann directs attention to the development of symptoms simulating intracranial tumor several months or years after an insignificant trauma of the skull: cortical irritation, intracranial pressure, papilledema and paralysis of the sixth nerve. X-ray may reveal a subdural hematoma on the surface of the parietal, frontal, or temporal lobes. Surgical results are satisfactory.

Hartmann has investigated *tonic pupils and absent tendon reflexes* (Adie's syndrome) which presents an Argyll-Robertson pupil not due to syphilis. The pupil reacts to light after a few minutes exposure to strong light and secondary dilatation is also slow. The pupil reacts to accommodation-convergence slowly and increases and persists

after accommodation-convergence has ceased. The pupils are usually dilated. The blood and spinal fluid Wassermann reactions are negative.

**Perimetry.**—J. Foster (Tr. Ophth. Soc. U. Kingdom 55:305, 1935) believes that alteration in the shape of the *color fields* is of slight significance when the field for white is altered.

**Phytopharmacological Method.**—D. I. Macht (Am. J. Ophth. 19:324 (Apr.) 1936) employs the following phytopharmacological method to study blood sera quantitatively: Seeds of *lupinus albus* are kept overnight in a beaker containing tap water. The next morning they are planted in finely divided moist sphagnum moss, then placed in the dark at room temperature. Seedlings, with roots measuring from 30 to 45 mm., are ready for experimentation on the third or fourth day. The length of the roots is measured with a millimeter rule and the seedlings are placed in an upright position in hard glass tubes containing the solutions to be studied. Controls are used. Other seedlings are placed in Shive solution containing 1 per cent. of normal or pathologic blood serum. The control seedlings and those in the various solutions are placed in the dark and incubated at a temperature of from 16 to 18 degrees C. for 24 hours. The length of the control seedlings and of the others is measured before and after the experiment. The increment in length of the roots of the seedlings in blood sera divided by that of the seedlings in the control solution gives the phytotoxic index. Human blood gives an average *phytotoxic index* of from 70 to 75 per cent.

Macht has found that the phytopharmacological method is useful in the differential diagnosis of *pemphigus* and *trachoma*. In both conditions a systemic toxemia is evidently present which can

be demonstrated by special pharmacological methods.

**Polarized Light.**—J. D. M. Cardell (Tr. Ophth. Soc. U. Kingdom 55:158, 1935) advocates the use of an ophthalmoscope which makes use of Nicol prisms to obtain polarized light. Polarized light eliminates corneal reflexes, permits a clear view of the macula through a small pupil, and facilitates ophthalmoscopic examination even when corneal and lenticular opacities are present.

**UNTOWARD EFFECTS OF PLASMOCIDE.**—S. V. Savelev (Sovet. vestnik oftal. 8:224, 1936) reports 19 cases of inflammation or atrophy of the optic nerve associated with symptoms of toxic encephalitis and edema of the brain as a result of the administration of "plasmocide" for the treatment of malaria.

**TREATMENT.**—*Radium.*—R. F. Moore (Tr. Ophth. Soc. U. Kingdom 55:3, 1935) emphasizes the value of radium in the treatment of intraocular lesions, particularly *bilateral glioma*. *Bilateral sarcoma* is practically unknown, but in cases in which the only eye or the better eye is involved, radium treatment is indicated if enucleation is refused.

Radon seeds filtered through 0.50 mm. of platinum are applied on the surface of the sclera, and are held *in situ* by sutures or by interstitial insertion.

Some of the *complications* of radium therapy are as follows: chemosis; excoriation of skin; loss of eyelashes and eyebrows; xerosis and necrosis of the cut edge of the conjunctiva; ulceration of the cornea and sclera; changes in the retina, choroid and lens; contraction of the orbital tissues; and chorioretinitis.

**EYE DISORDERS.—AMBLYOPIA.**—*Diagnosis.*—For the detection of malingering, L. Jese (Klin.

Monatsbl. f. Augenh. 96:71 (Jan.) 1936) proceeds as follows: He directs the patient to keep both eyes open. He changes the lenses in the trial frame on both sides at the same time. A plus 10 D. spherical lens is placed before the poor eye, and a plus 1.00 D. before the good eye. The vision and refraction of the good eye are determined by slight changes. The value of the lens before the poor eye is gradually reduced, while that before the good eye is increased, so that after about 5 changes the patient has either a correcting or a plano lens before the poor eye and a plus 10 D. lens before the good eye. The patient indicates the vision of the poor eye with and without glasses without being aware that the lenses have been "switched."

**Etiology.**—F. Soriano and J. Malbran (Arch. de oftal. de Buenos Aires 11:222 (Apr.) 1936) prefer to apply the term *toxic amblyopia* to those cases which are inflammatory and "retrobulbar neuritis" to those which are non-inflammatory in origin. They report a case of toxic amblyopia which resulted from the prolonged use of *hair dye* which contained acetate of lead; and another case in which opaque hair was seen roentgenologically. The latter case presented bilateral central scotomas, and postneuritic optic atrophy. It is probable that a lead compound had been used previously, because the hair dye in this case contained only silver.

S. Y. Lokshina (Sovet. vestnik oftal. 8:464, 1936) points out that methyl alcohol is present in tobacco leaves and in prepared tobacco and that it may be an important factor in the production of *tobacco amblyopia*.

**Treatment.**—H. C. Orr. (Brit. M. J. 2:69 (July 11) 1936) obtained improvement in 3 cases of chronic and 1 case of acute *tobacco amblyopia* by injections of 0.1 Gm. ( $1\frac{1}{2}$  grains) of ace-

tylcholine intramuscularly every day for a period of 1 month.

**ANISEIKONIA.**—According to Ames, aniseikonia (incongruity between the ocular images of the two eyes) is evidenced by the symptoms usually associated with ametropia, impaired or false binocular stereopsis, and in extreme cases by complete absence of fusion.

An ophthalmo-eikonometer is used to exclude, detect, and measure the amount of inequality in the size of the images. **Iseikonic lenses** are employed to magnify the smaller image so that both images on the retina may be equalized. Binocular fusion, stereopsis and relief from symptoms usually result.

**ASTHENOPIA.**—As a result of the study of 100 cases of asthenopia, S. I. Friedman (Sovet. vestnik. oftal. 8:110, 1936) found that the incidence of astigmatism against the rule was high; that the average size of the angle gamma is greater in astigmatism against the rule than in astigmatism with the rule; and that a small amount of astigmatism against the rule caused asthenopia and therefore should be corrected.

**CONTUSION.**—*Sequelæ.*—M. Davidson (Am. J. Ophth. 19:757 (Sept.) 1936) discusses the minor sequelæ of contusions of the eyeball. He studied 34 cases in which minor contusions had occurred and observed the sequelæ in the cornea, pupillary reflexes, iris, lens, vitreous, fundus, and visual acuity. This has been called the *anterior-segment traumatic syndrome of Frenkel*.

He advocates slit lamp "diapupillary" iris transillumination. At a distance of 25 cm. the slit lamp beam is directed into the pupil, having the slit lamp arm as close as possible to your head, the beam for the plane of the pupil is then focused so that it occupies only a portion of the pupil; the free portion furnishes a fundus reflex. This procedure

brings out even the most minute depigmentations of the iris.

Brown deposits on Descemet's membrane do not form part of the contusion syndrome. They are diagnostic of iritis and uveitis. D-shaped traumatic mydriasis is the most frequent sequel of contusion of the eye. The pupil becomes sluggish to all reactions. Davidson prefers the term traumatic iridoplegia, because not only the sphincter but the dilator is involved.

Single or multiple, confluent, round or irregular lesions of the root of the iris may be radial without involving the sphincter. Dehiscence of the pigment layer of the iris is frequently observed.

Opacities and subluxations of the lens occurred in 60 per cent. of the cases.

Bright red, rather large retrolenticular pigment particles occurred in 56 per cent. of the cases. Foveal whitish or pigment stippling and parafoveal yellowish or slightly pigmented small patches, and lesions at the periphery of the fundus which simulate anterior chorioretinitis or atypical retinitis pigmentosa occurred in 58 per cent. of the cases.

Davidson concludes that the lesions are anatomically related to each other. They stretch from the root of the iris along the equator of the lens, zonule, ciliary body, ora serrata, and vitreous. In this way they justify the anterior segment traumatic syndrome of Henri Frenkel.

Traumatic iridoplegia was the most frequent and the most readily demonstrated lesion. The other lesions occurred in about 50 per cent. of all cases.

**DYSTROPHIES, BONY.**—A. Sorsby (Tr. Ophth. Soc. U. Kingdom 55:499, 1935) discusses the ocular lesions which occur in bony dystrophies. He advocates Waardenburg's classification of cranial deformities. Oxycephaly presents 3 other clinical varieties, acrocephalosyndactyly (Apert), craniofacial

dysostosis (Crouzon), and hyperteloris, i. e., abnormal distance between two similar organs (Greig). The ocular lesions associated with digital abnormalities are: (1) arachnodactyly; (2) syndactyly with aniridia; (3) polydactyly with retinitis pigmentosa; (4) Lawrence-Moon-Biedl syndrome; (5) brachydactyly with microcornea; (6) lobsterhand with aniridia; (7) dystrophy of hands and feet with macular coloboma.

**HEADACHE.**—*Etiology.*—In a discussion of headache from the point of view of the ophthalmologist, W. H. Crisp (Am. J. Ophth. 19:93 (Feb.) 1936) states that according to H. Campbell, headache might arise in any of the following structures: (a) the brain; (b) its membranes; (c) the skull bones, including the mucous membranes which line the nasal and mastoid sinuses; and (d) the scalp. Headache is usually due to several causes. Frontal and parietal headaches or aches in and around the eyeball are usually characteristic of eyestrain, but occipital and nuchal pains are also frequently symptomatic of eyestrain. Headache due to eyestrain comes on during use of the eyes for close work, or for distance, as in watching a theatrical performance or in driving.

Although headache which occurs in the morning, or during the night, does not usually arise from eyestrain, in some cases it may result from eyestrain of the previous day.

Headaches may also be caused by encephalitis, intracranial tumor, meningitis, cerebral arteriosclerosis, sinusitis, nephritis, toxemia of tuberculosis, general fatigue, and errors of refraction (low errors of myopia, myopic astigmatism, and undercorrected hyperopia).

Uncorrected hyperopia, astigmatism, or improper correction may produce reflex symptoms such as nausea, vomiting,

dizziness, inability to concentrate, and peculiar sensations in the head.

Headaches may result from faulty habits of reading, e. g., rapid reading, reading in the presence of distraction, faulty angle or improper distance of the reading material.

Headache may also be caused by irregularities or indiscretions in diet, disorders of digestion, chronic gastrointestinal disease, allergic reaction, alcohol, tobacco, and by disturbances of digestion resulting from fatigue and emotional disturbances.

*Migraine* is usually regarded as "a paroxysmal affection comprising severe unilateral headache, preceded by visual phenomena and followed by nausea and vomiting," but Critchley and Ferguson state that the diagnosis may still hold good even if any one or even any two of these classical symptoms are absent. Allergy and heredity are factors in the production of migraine. Heredity may be evidenced by a family history of asthma, eczema, hay fever, urticaria and migraine or specific sensitivity to some particular substance.

**HEMIANOPIA.**—*In Brain Tumors.*—T. H. Johnson (Am. J. Ophth. 19:823, 1936) interprets his findings in 49 cases of homonymous hemianopia in verified cases of brain tumor, as follows: (a) a lesion at some point posterior to the chiasm produces a complete or sectoral homonymous field defect; (b) in lesions of the temporal lobe crescentic defects occur as frequently as quadri-sectoral defects and the majority of the hemianopic defects are incomplete. (c) In lesions of the occipital and frontal lobes, complete hemianopia is more frequent.

**INJURIES.**—C. Berens points out that not only scars of the cornea resulting from injury or disease but opacities in the lens resulting from slight injuries frequently clear up entirely after a long

period of time. In cases which present multiple foreign bodies of the cornea, it is not advisable to attempt removal of many at one time.

L. Jese (Klin. Monatsbl. f. Augenh. 96:110 (Jan.) 1936) describes some rare eye injuries: (a) A kick over the left eye resulted in an abscess of the orbit. Incision revealed the presence of a shoe nail and pus. (b) A tumor below the right upper orbital margin revealed an awn of wheat. It had perforated the conjunctiva and had migrated into the orbit. (c) In a patient with lagophthalmos the eye was lacerated by the teeth of a rat. The eye healed, but 4 years later enucleation was performed to relieve painful phthisis bulbi. (d) Two caterpillar hairs were seen in the stroma of the cornea of an eye which had been struck with a stone. After surgical removal, microscopic examination revealed bombyx hairs with hooks and a brown medullary cavity. Good vision resulted.

**Asthenopia.**—V. Wescott (Am. J. Ophth. 19:385 (May) 1936) points out that the discomfort and fatigue experienced in reading as a result of an injury to the head are not due to loss of accommodation. Sixty-five per cent. of 72 patients who had sustained injury to the head had a normal accommodative power. Although fracture may be absent, injury of the brain tissue may be present. He concludes that a disturbance in the organization of the function of reading, not a loss of accommodation, is responsible for the discomfort experienced in reading, following injury to the head.

**Cranial Trauma.**—Aubineau (Ann. d' ocul. 173:205 (Mar.) 1936) points out that a commotional subjective syndrome may appear in cases which present no demonstrable damage following cranial trauma accompanied by loss of consciousness. The syndrome may result from microscopic lesions in the

brain, corticomeningeal adhesions, vasomotor disturbances, alterations of the cerebrospinal fluid, or from other obscure causes. The disturbances may be (a) visual, *e. g.*, vertigo and displacement of objects may be produced by physical exertion or by a change in the position of the head; (b) asthenopic, *e. g.*, fatigue and occasionally slight ptosis may be produced by fixation.

#### **NASAL NERVE SYNDROME.**

**Etiology.**—Two cases of nasal nerve syndrome are described by C. C. Charlin (Ann. d' ocul. 173:25 (Jan.) 1936). Neuralgia and ulceration of the cornea were the respective predominant symptoms. In both cases relief was obtained after the use of tuberculin for diagnostic purposes. The reaction was positive. The glands at the hilus of the lungs were tubercular. Charlin believes that the syndrome was secondary to tuberculous toxins.

**MYOPIA.**—The London Board of Education, according to W. S. Knighton, recommends admission to sight conservation classes of young children whose myopia increases 1 D. a year. To arrest the progress of myopia the following have been recommended: good illumination, prevention of excess convergence, well-printed reading matter, rest periods, constant wearing of full refractive correction, general hygienic care, **calcium** and **parathyroid therapy**, instillation of **cycloplegic** in one eye to relax accommodation and to dissociate the eyes for near work and the empirical administration of **tuberculin** or **anti-luetic** drugs.

#### **NASOCILIARY SYNDROME.**

M. K. Soloveva (Sovet. vestnik. oftal. 8:108, 1936) reports a case of *Charlin's nasociliary syndrome* in a patient 48 years of age. The syndrome was characterized by pain in the eye, epiphora, circumcorneal injection, and neuralgia localized in the orbit. Relief was ob-

tained by the application of **cocaine** and **adrenalin** to the outer nasal wall.

**OTITIS, PURULENT.**—H. Tillé (Rev. oto-neuro-oftal. 11:31 (Feb.) 1936) discusses the ocular manifestations in purulent otitis and its complications. A lesion of the sixth nerve may indicate not only a Gradenigo syndrome, but also an abscess of the cerebellum or an intracranial hypertension. Involvement of the third, fifth, and sixth nerves is found in meningitis or cavernous sinus thrombosis. A lesion of the third nerve may indicate abscess of the temporoparietal lobe of the brain. Involvement of the fourth nerve is rare. Involvement of the fifth nerve may indicate anterosuperior petrositis. Papilledema may occur as a late complication of cavernous sinus thrombosis and abscess of the cerebrum or cerebellum. Because hypertension of the retinal arteries always precedes papilledema, the fundus should be studied during the course of otitis.

**SINUS DISORDERS.**—G. Worms (Arch. d'opht. 53:207 (Mar.) 1936) describes an interesting case of clinically undiagnosed suppurative sphenoidal sinusitis which produced inflammatory hypertrophy of the hypophysis and bilateral optic neuritis and resulted in death.

The condition occurred in an adiposogenital type of man, 21 years of age, who presented bilateral central scotomas followed by reduction of vision to 1/100 in each eye within 6 weeks, concentric contraction of the visual fields, dilated and almost paralyzed pupils, edematous optic disks, dilated veins and narrowed arteries. A diagnosis of pituitary tumor was made based on the clinical findings and the roentgenologically visible enlargement of the sella turcica with partial destruction of the posterior clinoid processes. The patient refused surgical treatment. After radiotherapy the headaches decreased but optic atrophy with blindness developed within 2 months. The patient died from meningitis 6 years later. Autopsy revealed adhesions between the

optic nerves and chiasm and the base of the brain, enlarged hypophysis surrounded by pus, basal meningitis, perforation of the posterior superior portion of the sphenoid sinus, and both sphenoids were filled with polyp and pus. A section of the hypophysis presented chronic inflammatory reaction but no adenoma.

Worms is of the opinion that the sinus infection was entirely responsible for the inflammatory enlargement of the hypophysis and the bilateral optic atrophy.

**SYSTEMIC DISEASES.**—*Ophthalmoscopy.*—Ophthalmoscopic findings, according to W. M. Yater (Am. J. Ophth. 19:302 (Apr.) 1936), may be divided into 5 groups: (1) Vascular changes in the retinas and the so-called retinitides. This group includes arteriosclerosis, nephritis, hypertension, and toxemia of pregnancy. (2) Changes which occur in cases of heart disease. (3) Changes in anemia, leukemia, and purpura hemorrhagica. (4) Changes in diabetes mellitus. (5) Changes which occur in diseases of the central nervous system.

Yater describes only the first 2 groups. (a) *Arteriosclerosis* is a degenerative disease of the blood vessels in which the large and medium-sized arteries are involved. Although arteriosclerosis is not a cause of hypertension, it is often associated with it. In arteriosclerosis of the retina a reduction in the caliber of the lumen of the arterioles and dimmed "light reflex" are present. Irregularity in width or diminution in total diameter which occurs in advanced hypertension is absent.

(b) Yater is of the opinion that *essential hypertension* arises from an abnormal sensitivity of the vasomotor system, probably of the vasomotor center in the medulla, so that all arterioles of the body are affected. At first there is hypertrophy of the muscular coat of the arterioles; later, degen-

erative changes (fibrosis of the arteriolar media and adventitia); and, finally, fibrosis and hyalinization of the intima and subintima, as a result of which the arteriolar lumina become smaller. The changes in the retina are as follows: narrowing of the arterioles; an irregularity of caliber (a definite sign of degenerative changes); increase of the luster of the "reflex stripe"; arteriovenous compression; increase in length and tortuosity of the arterioles; thrombosed arterioles appearing as thin white lines; thin white lines on the outer borders of the arterioles; and distention of the veins. Essential hypertension may be associated with so-called retinitis and neuroretinitis, due to vasoconstriction with reduction in the blood supply producing partial ischemia and stasis. Hemorrhages are common. Small superficial hemorrhages are linear and lie close to and parallel with the arterioles; the deeper ones are rounded. Hemorrhages are due to stasis in the capillaries.

White or yellow patches, which may be small and punctate or as large as the optic discs, are usually seen between the macula and the disc and below the disc. "Cotton-wool patches" represent areas of edema. These may resorb. "Hard," clean cut patches are probably cystoid spaces containing exudates. Glistening white deposits in the region of the macula are probably fats and lipoids. These rarely, if ever, disappear.

According to Yater, *neuroretinitis* is an advanced stage of retinitis. He believes that the onset of retinitis and neuroretinitis is due to a sudden increase in the degree of constriction of the arterioles. After the hypertensive crisis subsides, the changes in the retina other than those which are permanent may disappear.

(c) *Nephritis*.—There are 3 main groups of diseases of the kidney: (1) diffuse glomerulonephritis; (2) nephroses

(tubular degeneration); (3) degenerative vascular diseases. Hypertension is rarely present in nephrosis, but is present in groups 1 and 3. Neuroretinitis occurs late in the course of kidney disease and is an early sign of impending death. Albuminuria has no relation to retinitis.

(d) *Pregnancy*.—The following conditions may occur during pregnancy: night blindness; retinitis pigmentosa; contraction of fields of vision; hemorrhagic retinitis of pernicious vomiting; eclamptic amaurosis (probably due to edema of the visual centers in the cerebral cortex); and retinal changes in cases of toxemia with hypertension (due to vascular changes, *viz.*, a generalized arteriolar spasm). The earlier in pregnancy the retinitis appears, the poorer is the chance of obtaining a living child, and the greater is the danger of permanent vascular injury. However, there are cases in which retinitis does not recur with subsequent pregnancies.

(e) *Heart Disease*.—Ninety-six per cent. of cases of heart disease due to hypertension presented changes characteristic of disease in the retinal arterioles, particularly in cases in which the blood-pressure became normal. The retinal findings may indicate the diagnosis. Ninety-two per cent. of cases of heart disease due to coronary arteriosclerosis presented retinal vascular changes. Fifty per cent. of all cases of hypertensive heart disease develop coronary arteriosclerosis.

Yater concludes that retinal arteriosclerosis associated with heart disease indicates that the heart disease is due to hypertension or coronary arteriosclerosis or both, provided other causes are absent. Petechiæ with white centers are seen in subacute bacterial endocarditis.

**THROMBOPENIA.**—M. E. Parkhamenko (Sovet. vestnik oftal. 7: 244, 1935) reports a case in which the findings of a hemorrhage in the retina



of a man. 25 years of age, led to a diagnosis of thrombopenia. The diagnosis was established by examination of the blood and by capillaroscopy. The hemorrhages disappeared and vision was restored after x-ray therapy of the spleen had been administered.

**TUBERCULOSIS.—*Diagnosis.***—F. M. Meksina (Sovet. vestnik oftal. 8: 193, 1936) discusses *ophthalmotonometry* in the diagnosis of ocular tuberculosis. He ascertained that the intraocular tension rises 10 to 15 mm. within 1½ to 2 hours after the injection of tuberculin, then falls below the original intraocular tension 4 hours later, and usually lasts 2 or 3 days. The presence of glaucoma or detachment of the retina interferes with the diagnostic value of this reaction.

***Etiology.***—The relation between scrofulous and tuberculous disease of the eye is discussed by A. B. Katsnelson (Averbach Jubilee Volume, p. 196, 1935). He found that 91 per cent. of his series of patients with tuberculosis of the anterior segment of the eye and 10 per cent. with tuberculosis of the posterior segment, suffered from phlyctenular conjunctivitis during childhood. His findings were the result of his investigation of 37 cases of tuberculosis of the anterior and 37 cases of the posterior segment of the eye.

**VITAMINS.**—H. Viallefont and E. Diacono (Arch. d'opht. 52:723 (Oct.) 1935) discuss the rôle of vitamins in ophthalmology. They state that vitamins A and C are particularly important. Lack of vitamin A produces xerosis of the conjunctiva, keratomalacia and hemeralopia. They report that keratitis resulting from trophic disturbances, phlyctenular keratoconjunctivitis, and other lesions of the cornea which are slow in healing have yielded to local vitamin A therapy.

Lack of vitamin C produces scurvy without ocular disturbance, but may produce recurrent hemorrhages in the vitreous.

**EYEBALL.—BURNS.**—From an experimental study of *alkali burns* of the eyeballs of guinea-pigs, D. R. Vinogorov and R. Z. Kopit (Sovet. vestnik oftal. 8: 333, 1936) conclude as follows: Five per cent. solutions produce necrosis of the epithelium and endothelium of the cornea, and may result in edema of the retina and the formation of Greef cysts in the ciliary body. Subcapsular cataract may result from weak alkali solutions; necrosis of the eyelids, conjunctiva, cornea, ciliary body, iris and epithelium of the lens from strong alkali solutions. Descemet's membrane is resistant even to 50 per cent. solutions.

**ENOPHTHALMOS.**—D. G. Bushmich (*Ibid.* 8: 43, 1936) reports 3 cases of enophthalmos associated with retraction movements of the eyeball. In one case, attempted surgical correction revealed that the insertion of the medial rectus muscle was abnormally far forward, and that the lateral rectus muscle was represented by a thin fibrous band.

**EXOPHTHALMOS.**—A series of cases of exophthalmos associated with nervousness and tremor are reported by C. Weskamp and C. Alvarez (Ann. d'ocul. 173:273 (Apr.) 1936) in which, although the basal metabolic rate and the pulse rate were normal and no enlargement of the thyroid gland was detected, a fully developed form of *Basedow's disease* was present.

***Etiology.***—After reviewing the literature, E. Kraupa and K. Mendl (Ztschr. f. Augenh. 89: 40 (June) 1936) find that only 95 cases of *intermittent exophthalmos* have been reported in the past 65 years. In Kraupa's patient the eye protruded upon *stooping*. X-rays disclosed 2 phleboliths which advanced

0.5 cm. when the eyeball protruded. Protrusion results from filling of the blood spaces in varices and angiomas. It is often associated with pulsation.

M. Cohen (Arch. Ophth. 15:457 (Mar.) 1936) reports 4 cases of inflammatory exophthalmos which were associated with catarrhal disorders of the accessory sinuses. Case 1 began as a furunculosis of the ala nasi, spread to the orbit, accessory nasal sinuses, and cavernous sinuses and resulted in death. Case 2 began as a nonsuppurative cellulitis from subacute ethmoiditis and subsided after local treatment of the eyes and nose. Cases 3 and 4, which were chronic, were relieved by a Krönlein operation.

**FOREIGN BODIES.—Localization.**—In the localization of intraocular foreign bodies J. Zuckerman points out that this may be done by direct observation, ophthalmoscopy, biomicroscopy, the use of the sideroscope (if the foreign body is magnetic), the subjective sensation of pain when the magnet is applied and by x-rays.

The intensity of the shadow cast by a foreign body decreases in the following order: lead, steel, iron, copper, brass, stone, pencil lead and glass.

X-ray will reveal a particle of iron or steel even as small as 0.1 mm.

Among the various devices for assisting in the localization of intraocular foreign bodies are the following:

(a) Application to the cornea of a contact glass which has 4 lead marks. Two exposures, one anteroposterior and the other lateral, are taken.

(b) Insertion as deeply as possible into the orbit of a dental film, first nasally to obtain a lateral view and then inferiorly to obtain a view from above.

(c) X-ray of artificially proptosed eye. Proptosis may be produced by the injection into Tenon's capsule of 1 drop of a 40 per cent. solution of iodopin

with as much air as possible by means of a 20 c.c. syringe, or the injection retrobulbarly of several c.c. of a solution of 1 per cent novocaine. H. E. Thorpe advocates the use of an endoscope 3 mm. in diameter (similar to a urethroscope) for the removal of foreign bodies.

**Treatment.**—L. von Blaskovics (Ztschr. f. Augenh. 88:75 (Jan.) 1936) recommends cyclectomy (1) in prolapse of the ciliary body, (2) in rupture of the sclera, (3) as a preliminary to extraction of a nonmagnetic foreign body in or behind the ciliary body.

The conjunctiva is incised meridionally and undermined to the margin of the cornea. A meridional incision is made half through the sclera and horse hair sutures are inserted, the scleral incision is completed and the ciliary body is freed 2 or 3 mm. to the right and left of the incision. The ciliary body is grasped and its projecting part is excised.

**Magnet extraction** of the intraocular foreign bodies is discussed by A. W. Morse (Am. J. Ophth. 19:40 (Jan.) 1936). He concludes as follows: When the eye is injured, the presence of an intraocular foreign body should always be suspected. An x-ray examination is not necessary if removal can be performed through the original wound, the anterior route, the posterior route at a selected spot, or between the inferior rectus and lateral or medial rectus and between the ciliary body and the ora serrata.

An x-ray examination is necessary in those cases in which there is no response to the magnet, the foreign body cannot be brought to the selected spot posteriorly, removal of the foreign body by means of the magnet has failed, when the condition is of long standing, and to confirm the diagnosis.

If the entrance wound is large, extraction of foreign body should be performed through it; if small, through the anterior route.

If the foreign body cannot be brought into the anterior chamber, or, if it is large, extraction by the posterior route at a selected spot is advocated in order to avoid bleeding, injury to the vitreous and detachment of the retina.

Quint (Klin. Monatsbl. f. Augenh. 96: 371 (Mar.) 1936) summarizes the results of his experiences with **magnet extraction** of intraocular foreign bodies as follows: After extraction by introduction of the magnet into the vitreous, 20 to 30 per cent. of cases resulted in detachment of the retina, 40 per cent. in enucleation secondary to uveitis and panophthalmitis, and 20 per cent. in useful vision. He advocates the use of the sideroscope and x-rays for diagnosis, the careful incision of the sclera, and the application of the giant magnet to the wound. If the foreign body is elongated, he cautions against drawing it into the anterior chamber.

In order to *prevent postoperative complications* in magnet extraction of intraocular foreign bodies, Sellas, Jr., recommends the administration of **foreign protein** and the subconjunctival injection of a solution of **cyanide of mercury** (2:1000 to 5:1000).

**GLAUCOMA.—Treatment.**—E. de Grósz (Arch. d'opht. 53:25 (Jan.) 1936) **ionized** 14 patients, using **glaucozan** in dilutions of from 1:250 to 1:1000, and a current of 1 milliamperes for 1 minute. Ionization is better than instillation because it is more rapid, less painful with the weak dilutions, and is unaccompanied by the effects of absorption. Two treatments were usually necessary. Treatment is contraindicated in primary and in hemorrhagic glaucoma.

**Iridocorneosclerectomy** for glaucoma is advocated by C. Berens (Am. J. Ophth. 19:470 (June) 1936).

After preparation and local anesthesia, the conjunctiva at the upper limbus is ballooned with **adrenalin-novocaine solution**. A

slightly curved incision 15 mm. long concentric with the limbus is made in the conjunctiva down to the sclera 10 mm. from the limbus. This flap is dissected from the sclera down to the cornea, and the layers of the cornea are dissected into by means of a side-to-side movement with a flat sharp spud with a rounded end. The point of a blunt spatula should then extend 1.5 mm. into the cornea. An incision is made with a broad hollow-ground keratome, starting in the sclera 1.5 mm. above the limbus and extending into the anterior chamber until the wound is 4 mm. long.

The angles of the scleral wound are extended toward the limbus until the incision is approximately 5 mm. long. The sclera and cornea are clipped with a punch as deep within each angle as possible; the remaining lip of sclera and cornea are then clipped, so that a serrated edge results.

A two-cut glaucoma iridectomy is made. After the first snip the iris is torn from the ciliary body by traction forward and toward the uncut side. The pillars are replaced.

The conjunctival wound is closed with an over-and-over running catgut suture (0000 plain), enclosed by a double bite in the conjunctiva, temporally in the right eye, and nasally in the left eye, and then the wound is closed, anchored in a corresponding position nasally or temporally and so that the anchored ends will be slightly above the highest point of the conjunctival incision. The wound edges, except at the extremities, are crushed with forceps; a grooved spatula is inserted in one angle and an anterior chamber irrigator in the opposite angle. Blood and fibrin are washed out. Sufficient half-normal physiologic **saline solution** is allowed to remain under the flap to balloon it forward. The extremities of the wound are now crushed with forceps. One drop of 3 per cent. **atropine** is instilled. **Massage of the eyeball** is begun 3 times a day from 24 to 48 hours after operation. The patient is placed in bed with his head elevated but is allowed out of bed the day following operation.

**Iridocorneosclerectomy** is applicable to all forms of acute and chronic glaucoma, whether primary or secondary. Successful results were obtained in 86.8 per cent. of 38 unselected eyes with primary glaucoma, in 73.1 per cent. of the 26 eyes with secondary glaucoma,

and in 75 per cent. of 4 eyes with acute glaucoma.

O. R. Wolfe and M. J. Blaess (*Ibid.* 19:400 (May) 1936) recommend the **seton operation** for glaucoma. Their technic is as follows:

A curved incision 8 mm. long concentric with the limbus is made in the conjunctiva 5 mm. from the cornea, below and nasally. The conjunctiva is undermined and the flap is turned back over the cornea. A similar flap is made temporally. A keratome is passed into the anterior chamber under the nasal conjunctival flap until a 3 mm. incision is made in the sclera just beyond the limbus. The conjunctival flap is then replaced. A similar incision is made with the keratome under the temporal flap. Both conjunctival flaps are turned back over the cornea. A straight, blunt-tipped lacrimal needle threaded with braided white silk is inserted into the anterior chamber from the temporal side and passed between the cornea and the iris to emerge on the nasal side. The lacrimal needle is then withdrawn. Each end of the seton is cut off about 4 or 5 mm. from the limbus and buried under the flap. The conjunctival wounds are closed with sutures. On the fifth day, the conjunctival sutures are removed.

This operation is particularly useful in absolute glaucoma. It is a simple method for the control of any secondary rise in tension that may occur.

**PHOTOGRAPHY.—Skeleton-free Method.**—R. C. Lennon (Klin. Monatsbl. f. Augenh. 96:234 (Feb.) 1936) obtains skeleton-free photography of the eyeball by pulling the eyeball forward by means of sutures passed through the insertions of the superior and inferior recti muscles. In this manner an exophthalmos of 8 mm. may be obtained and the eyeball may be drawn into any desired position.

**TENSION.—Mydriatics.**—H. S. Gradle (Am. J. Ophth. 19:37 (Jan.) 1936) studied the effects of mydriatics and cycloplegics upon intraocular tension in a series of 500 patients 30 years of age or older. He summarizes his find-

ings as follows: (1) In 2.8 per cent. of the eyes, the intraocular tension increased more than 5 mm. Hg. under mydriasis. (2) In 0.9 per cent. of the eyes with increase in tension, the presence of a preglaucomatous condition was diagnosed. (3) In 23.6 per cent. the tension became greater by 1 to 9 mm. Hg. in one eye than in the other. (4) Preglaucomatous conditions or incipient glaucoma could be diagnosed many months or years earlier if, in persons past the age of 30 years, tonometric measurements were made immediately before and after the use of a mydriatic or a cycloplegic.

**IRIS.—CYSTS.**—Four cases of familial and congenital cysts of the retinal pigment layer of the iris are reported by A. Cowan (Am. J. Ophth. 19:287 (Apr.) 1936), who states that these bilateral cysts were composed of pigmented masses and pouches filled with fluid. They projected from the posterior layers of the iris through the pupil and into the anterior chamber. When the pupil was contracted, they protruded farther into the anterior chamber. The cysts would empty and refill. In 1 case there was a history of mental deficiency and chorea; 3 cases were negative medically. Cowan is of the opinion that the condition is related to ectropion of the uvea.

**LACRIMAL APPARATUS.**—E. C. Ellett is of the opinion that the inflammation accompanying acute dacryocystitis may be mistaken for erysipelas when the entire side of the face is involved. Chronic dacryocystitis is usually due to obstruction in the tear duct. **Excision of the lacrimal sac** or external (West) or internal (Toti, Dupuy-Dutemps, Bourguet and Mosher) **dacryocystorhinostomy** is recommended.

**LENS.—CATARACT.**—Kirby points out that cataract is a degenerative change; the capsule of the lens is a selective semipermeable membrane. Moreover, the lens epithelium not only forms lens fibers, but probably secretes a substance which in conjunction with secretion from the epithelium of the ciliary body maintains the integrity of the dead lens fibers. Nuclear sclerosis is abnormal physiologic sclerosis, with dehydration and hardening of the lens fibers. In cortical cataract, the outer lens fibers are destroyed; this process is associated with hydration and swelling. Lens protein is hygroscopic. Vacuolation, splitting of sutures, and lamellar separation result from an excessive amount of water. The lens is nourished by the salt, sugar, protein, and oxygen content of the aqueous.

**Etiology.**—During a period of 2½ years P. J. Leinfelder and H. D. Kerr (Am. J. Ophth. 19:739 (Sept.) 1936) observed the eyes of several groups of rabbits which had been exposed to various doses of x-rays. They found that nonprogressive lens changes developed in all cases. These consisted of small punctate dots in the posterior polar region.

They also observed 5 patients who had been treated with x-rays in the region of the eyes. Two children developed cataracts 2 years after treatment; the 3 adults seen 30 months after irradiation had developed no opacities.

**Treatment.**—There is no specific medical treatment for the arrest or cure of cataract, according to Kirby. **Attention to general health and hygiene**, and sufficient supply and absorption of all **vitamins** are indicated. **Lens antigen** is of no value in the treatment of cataract. It is of assistance in desensitization of patients against endophthalmitis phacoanaphylaxis and in absorption of post-operative remains of lens cortex.

The use of **gravidan** for the treatment of cataract and glaucoma is recommended by S. M. Khayutin (Sovet. vestnik oftal. 8:174, 1936). He has found that this preparation of the urine of pregnant women improves visual acuity, reduces tension, increases the field of vision in glaucoma, and arrests the progress of incipient cataracts.

M. Khalil (Brit. J. Ophth. 20:167 (Mar.) 1936) performs **extraction of cataract by the electro-diafaco method**. The electrode handle consists of a capillary glass tube inside of which are 2 fine steel movable wires of 0.14 mm. diameter. These are made to protrude about 2 mm. beyond the tube. The wire is protruded and rested on the lens capsule without penetrating the lens. Between 80 and 90 ma. of current is applied for 1 second. The lens becomes coagulated and adherent to the electrode and may be readily extracted.

**SURGERY.**—Kirby recommends: (1) **Akinesis**, by blocking the branches of the facial nerve or by local infiltration anesthesia with **procaine** into the constrictor muscles surrounding the orbit. (2) **Immobilization of the extraocular muscles** by deep injection into the orbit or by injection or suture of only the superior rectus muscle. (3) **External canthotomy** in indicated cases to avoid pressure which may result in loss of vitreous.

Kirby points out that the results of operations for reattachment of the retina in aphakic eyes are not usually successful.

E. Seidel (Arch. f. Ophth. 135:159, 1936) states that after **extraction of cataract**, remains of lens fibers are less irritating than the repeated entering of the eye with instruments to remove them. He performed 200 extracapsular cataract extractions with **iridectomy**, leaving all possible remains of lens in the anterior chamber, but healing took place without inflammation. In order to avoid inflam-

matory reaction, he even avoids iridectomy and prevents prolapse of the iris by the instillation of a solution of **eserine** (1 per cent.) immediately after the operation. He believes that because the posterior lens capsule is removed in intracapsular extraction the vitreous is exposed to a greater possibility of infection. Tears in the retina and a tendency to detachment of the retina may result because the lens is torn from support by the ciliary epithelium and the anterior part of the retina. His procedure is as follows:

A solution of **atropine** (1 per cent.) is instilled 1 hour preoperatively; a solution of **cocaine** (10 per cent.) 5 or 6 drops, with 2 drops of **adrenalin** are instilled at 1 minute intervals at the time of operation. A conjunctival flap and corneal section are made. Forster's capsule forceps and the iris reposer are the only instruments which enter the eye. To prevent secondary cataract, he advises grasping and removing with the capsule forceps as large a part of the anterior lens capsule as possible.

H. R. Hildreth (Am. J. Ophth. 19: 770 (Sept.) 1936) advocates the use of a **fluorescent lamp** for cataract surgery. The surface of the lens and the particles of cortex become fluorescent and readily visible by means of long-wave ultraviolet rays. This form of illumination is of assistance in localizing and grasping a lens which has become dislocated into the vitreous and in detecting particles of cortex. These can be expelled by irrigation in order to prevent secondary cataract. Short-wave ultraviolet rays, obtained by means of a suitable filter, are used for treatment of disease of the cornea and conjunctiva. The fluorescent lamp has several additional uses. Infrared rays can be obtained by means of filters for photography of the eye with infrared films, or a red-free light may be obtained for red-free ophthalmoscopy.

*Complications.*—H. W. Woodruff (*Ibid.* 19:146 (Feb.) 1936) discusses the management of complications in the operation for *senile cataract*:

(a) *Prolapse of Vitreous.*—If the vitreous is fluid, he follows the suggestion of Harold Gifford to perform needling several times rather than to attempt immediate extraction. The loss of normal vitreous can best be avoided by the van Lint method of akinesia of the eyelids. If the vitreous prolapses in the absence of conjunctival suture, the eye should be closed at once. If the prolapse of normal vitreous occurs before extraction, it is better to discontinue the operation and to remove the lens at a subsequent operation.

(b) *Expulsive Hemorrhage.*—He points out that **avertin anesthesia** lowers the blood-pressure and the intraocular tension. Removal of the eye is not necessarily indicated in these cases. Sometimes a normal eyeball may be retained.

(c) *Intraocular Hemorrhage.*—Intraocular hemorrhage which occurs postoperatively can be arrested by the subcutaneous injection of **adrenalin** and **ergot**.

(d) *Intraocular Infection.*—If discovered within 24 hours, this may be combatted by the injection into the orbit of 8 or 10 mm. of a solution of **cyanide of mercury** (1:1000), with 4 minims (0.25 c.c.) of 4 per cent. **cocaine** (to prevent pain).

The eye should be examined on the day after the operation. Woodruff frequently injects **foreign protein** at the time of operation.

(e) *Postoperative Glaucoma.*—The intracapsular method of operation prevents the development of glaucoma. Epithelial ingrowth may cause glaucoma. Foreign substance in the wound and roughness of the edge of the knife should be avoided.

(f) *Late Iris and Vitreous Prolapse*.—This condition can be avoided by a **protective bandage**.

(g) *Retinal Detachment*.—He believes detachment is due to anterior choroiditis arising from tuberculosis or from focal infection. Treatment with **tuberculin** is advocated, even if the skin test is negative.

(h) *Irritation from Retained Cortex*.—This condition can be *prevented* by **thorough removal of cortex**. Alternate use of **atropine** and **eserine** is of assistance.

(i) *Sympathetic Ophthalmia*.—This condition is a rare complication.

(j) *Central Corneal Opacity*.—This is probably due to interference with corneal nutrition.

(k) *Fistula*.—This is corrected by a **conjunctival flap** over the fistula after the fistula and the under surface of the flap have been **cauterized with silver nitrate**.

Woodruff concludes that a general physical examination and examination of both eyes should be made and the pupillary reactions and intraocular tension studied preoperatively. He recommends: (1) **intracapsular operation** for *immature lenses* in people over 55 years of age; (2) **capsulotomy** in *mature cataracts* regardless of age; (3) **capsulotomy and irrigation** in people under 55 years of age, having *immature lenses*. **Conjunctival sutures** should be inserted. **Complete iridectomy** should be performed.

D. Vail (Arch. Ophth. 15:270 (Feb.) 1936) describes a case of *epithelial downgrowth* into the anterior chamber following cataract extraction. The growth of epithelium was arrested by the application of **radium**. Based on his experimental findings, Vail states that **x-rays** are more effective for the destruction of newly-developed epithelial cells

In a case of *epithelialization* of the anterior chamber following cataract extraction, A. Fazakas (Ztschr. f. Augenhe. 88:315 (Mar.) 1936) obtained a cure by the use of a **steam cautery**. He reopened the wound, grasped the thin pellicle with forceps, separated the lips of the wound, and applied the steam cautery. The eye healed and has remained unchanged for 4 years.

C. S. O'Brien (Arch. Ophth. 14:527 (Oct.) 1935) points out that *detachment of the choroid* occurs almost invariably at the time extraction of cataract is performed. Reattachment of the choroid usually takes place and central and peripheral vision are not affected. No treatment is necessary.

**MUSCLES.—ANISOPHORIA.—Treatment.**—J. S. Friedenwald (Arch. Ophth. 15:283 (Feb.) 1936) describes 3 methods for the correction of anisophoria, a condition in which the muscular imbalance varies with direction of gaze: (1) the use of segments of prisms; (2) displacement of reading matter toward the side of the eye which has the greater amplitude of rotation; and (3) magnification of the image for the eye which has the greater amplitude of rotation.

**EXAMINATION.—Screen Test.**—J. W. White (Am. J. Ophth. 19:653 (Aug.) 1936) discusses the applications of the screen test and its modifications; screen-Maddox rod, and screen-comitance for the diagnosis of muscle imbalances. He draws attention to the following advantages of the screen test: it is objective, precise, accurate; applicable to phorias and tropias; not dependent on binocular vision; quickly applicable even to children; and it is the only test that is applicable in all cases in which vision is sufficient for central fixation.

He points out that some cases of strabismus change from convergent to divergent when a vertical deviation is present. In some patients this followed operation for the correction of a lateral deviation without correction of the vertical deviation. This change also developed in cases in which operation was not performed.

He explains that exophoria may result from (1) weakness of one or both interni; (2) overaction of one or both externi; (3) underaction of the convergence power; or (4) excess of the divergence power. To determine which of these factors is responsible, he proceeds as follows:

He repeats the test for near when the eyes are turned first to the right and then to the left. If exophoria (or exotropia) is greater for distance than for near and is not increased in looking to the right or left, primary divergence excess is present. If exophoria (or exotropia) is greater for near than for distance and it does not increase when the eyes are turned to the right or left, convergence insufficiency or convergence paralysis is present. If exophoria increases in looking to the right, paralysis of the left internus or spasm of the right externus is present. If deviation increases in looking to the left, paralysis of the right internus or spasm of the left externus is present. If exophoria or exotropia increases in looking to both the right and to the left, paralysis of both interni is present. Exophoria or exotropia of a divergence excess or of a convergence insufficiency is never greater in looking to the right or left than it is in the primary position.

Esophoria may result from (1) divergence insufficiency or paralysis; (2) convergence excess or spasm; (3) a weak external rectus; or (4) an overactive internal rectus. The responsible factor (as described in exophoria) is determined by measuring the amount of deviation for distance, near and when looking to the right and to the left.

Right hyperphoria may be produced by an excessive power of sursumvergence, underaction of the depressors, or

overaction of the elevators of the right eye, or, on the other hand, by underaction of the elevators, or overaction of the depressors of the left eye. In left hyperphoria, the opposite is the case. In order to determine which muscles are involved, deviation should be measured in the upper and lower corners. Primary paralyses are common, primary spasms infrequent. Secondary contractures of direct antagonists and secondary deviations of associate muscles are common.

In order to make a definite diagnosis, the amount of deviation should be measured for distance and for near and in the 6 cardinal positions.

The deviation for distance and near in the 6 cardinal positions is measured by placing prisms (1) base in, for exophoria or tropia, to stop all movements, or slightly to overcorrect and then deducting 1 or 2 prism diopters; (2) base out, for esophoria or esotropia; (3) base down before the right eye, or base up before the left eye, for right hyperphoria or hypertropia, and the reverse for a left hyperphoria or hypertropia.

When lateral and vertical deviations are combined, one prism is held base up or down, while another is held base in or out, to correct both deviations. The lateral deviation often is decreased when the vertical deviation is corrected.

White recommends the use of the screen-Maddox-rod test for vertical deviations. The rod is placed vertically before one eye. This eye is screened and uncovered and the patient is directed to indicate the position of the light streak. Prisms are placed before the eye to cause the image of the rod to bisect the spot of light when the screen is first removed.

He also recommends the screen-comitance test (performed in the 6 cardinal directions) as follows: The movements of both eyes are observed behind the



screen while each eye in turn is screened and while the other eye fixates. A vertical deviation often is the cause of the lateral deviation.

**Maddox Rod and Prism.**—For the detection of vertical imbalance, C. Berens (Brit. J. Ophth. 19:661 (Dec.) 1935) recommends the use of a red multiple Maddox rod to which a 0.75 diopter prism has been added. The prism is placed with its base at right angles to the rod. If no vertical imbalance is present, by rotation of the prism, the line will appear alternately above or below the light at equal distances. If the red streak of light is seen on a level with the light, hyperphoria is present. This addition to the Maddox rod is of value in rapidly eliminating low degrees of hyperphoria and in the detection of malingering.

**REFRACTION.—Aniseikonia.**—E. J. Ludvigh (Am. J. Ophth. 19:292 (Apr.) 1936) suggests that the method employed to diagnose aniseikonia may be faulty and that the relief of symptoms obtained by the lenses prescribed may be due to the correction of anisophoria, not of aniseikonia. He points out that great differences in the size of images between the two eyes occur normally during reading. He states that these are much greater than those which are usually corrected by "iseikonic" lenses. He is of the opinion that the symptoms may be psychoneurotic in origin. He also points out that a change of over 14 per cent. in the relative sizes of the foveal images of the two eyes may take place during the normal use of the eyes while reading a line of print.

**Presbyopia.**—C. E. Ferree and G. Rand (*Ibid.* 19:238 (Mar.) 1936) advocate the use of a variable illuminometer to assist in the correction of presbyopic eyes. A correcting lens should be prescribed that is most satisfactory for the range of intensities of illumina-

tion (from 5 to 20 foot candles). They point out that in refraction of presbyopic eyes the use of higher intensity of illumination than that at which the glasses are to be used will result in undercorrection.

**STRABISMUS.—Treatment.**—The nonsurgical treatment of nonparalytic strabismus is discussed by S. V. Abraham (Am. J. Ophth. 19:139 (Feb.) 1936), who also attempts to explain the probable causes of successes and failures. He presents the results obtained from an analysis of 66 cases of nonparalytic strabismus without ocular pathology, 23 cases of nonparalytic strabismus with ocular pathology, and 200 nonpathologic cases of unilateral and bilateral amblyopia without strabismus.

He considers general health an important factor in the production and recurrence of strabismus and in the prevention of response to orthoptic training. Five of 10 cases of intermittent strabismus resulted from a disturbance of the general health. The strabismus disappeared with improvement of the general health. He suggests that in the nonsurgical treatment of strabismus, the following errors of refraction should be considered: (a) hyperopia of 3.00 diopters or more; (b) astigmatism of 1.50 diopters or more; and (c) anisometropia of at least 2.00 diopters.

**Inequality in visual efficiency** should be corrected before fusion training is attempted. He reports that J. B. Feldman (Arch. Ophth. 13:419 (Mar.) 1935) usually developed the vision in the poorer eye to  $20\%$  before starting fusion treatment. He suggests electrical stimulation of thinned, stretched, or atrophic muscles.

**OPTIC NERVE.—DISEASES OF.—Diagnosis.**—H. Gasteiger (Klin. Monatsbl. f. Augenh. 96:589 (May) 1936) reports that in 6 cases of doubtful

affections of the optic nerve, antero-posterior, bitemporal and stereoscopic x-ray pictures of the skull revealed calcification and arteriosclerosis of the blood vessels (particularly of the internal carotid). Loss of vision resulted from trophic disturbance or pressure on the optic nerve.

**Treatment.**—V. Much (Ztschr. f. Augenh. 89:58 (Apr.) 1936) treated 8 cases of disease of the optic nerve by inhalations of **amyl nitrite**. Five of these patients had retrobulbar toxic amblyopia due to alcohol or tobacco. He obtained improvement in every case and complete cure in 6 cases. He attributed the beneficial effects to vasodilatation resulting in hyperemia of the choroid and retina, with improved metabolism of the tissues.

**ATROPHY.—Treatment.**—G. Springowitsch (Klin. Monatsbl. f. Augenh. 96:342 (Mar.) 1936) reports beneficial results from retrobulbar injections of 0.5 c.c. (8 minims) of a **solution of atropine 1:1000** in optic atrophy regardless of etiology. The improvement in vision is attributed to vasodilatation. The resulting hyperemia stimulates the function of any remaining living nerve fibers.

E. Heinsius (Ztschr. f. Augenh. 87:298, (Nov.) 1935) obtained excellent results in tabetic optic atrophy by treatment with malaria. He states that active cases of atrophy of the optic nerve can be arrested completely or at least for a few years. He urges **malarial therapy** despite its dangers, because this is the only therapy from which such good results have been obtained.

**ATROPHY, SYPHILITIC.—Treatment.**—In an attempt to control optic atrophy due to syphilis, C. P. Clark (Arch. Ophth. 15:250 (Feb.) 1936) induced **malaria** in the treatment of 8 patients afflicted with tabes, 2 with dementia paralytica and 2 with dementia paralytica of the tabetic form. Eight

patients improved, in 4 patients the optic atrophy was too far advanced to expect improvement and one was unchanged. In the treatment of syphilis, malaria acts by producing fever, vasodilatation, increased body metabolism and stimulation of the reticulo-endothelial system.

J. Sobanski (Arch. f. Ophth. 135:401, 1936) has found that tabetic atrophy of the optic nerve takes place when the diastolic pressure in the central artery of the retina is less than twice the intraocular tension. In addition to **anti-syphilitic treatment** and **tonics**, he administered **miotics** and performed **cyclodialysis** (in 24 eyes) and **cyclodialysis combined with iridencleisis** (in 1 eye) in a series of 33 patients, 20 of whom were totally blind in 1 eye. Thirty-six of 46 eyes which had some vision were improved, 5 were unchanged, and 5 became worse.

**CHOKED DISC.—Etiology.**—W. Kyrieleis (Arch. f. Ophth. 135:100, 1936) points out that papilledema associated with increased intracranial pressure arises from an active force lying outside the eye, while papilledema without increased intracranial pressure arises from passive factors located in the eye; *e. g.*, venous stasis, abnormal permeability of the vessel wall as a result of vasomotor or osmotic disturbances, or stasis of tissue fluid.

**OPTIC NEURITIS.—Etiology.**—R. R. James, St. C. Thomson, L. Colledge and H. C. Hodgson (Brit. J. Ophth. 20:164 (Mar.) 1936) report a case of acute unilateral retrobulbar neuritis associated with diseases of the nasal sinuses. This condition occurred in a man 72 years of age who had a suppurating left antrum. Drainage was obtained through the socket of a tooth. Sudden blindness of the left eye with a large central scotoma developed 3 years later. X-ray revealed thickening of the mucous membrane of the left antrum,

frontal sinus, and posterior ethmoid, with the presence of a "fluid level" in the sphenoid. In spite of drainage of the sphenoid and ethmoid, no improvement in vision was obtained. Infection had apparently taken place directly through the wall of the sinus into the optic nerve. The right eye was not involved.

As a result of his observation of 5 patients affected by retrobulbar neuritis resulting from chronic sinusitis, F. Durando (Riv. oto-neuro-oftal. 12: 675 (Sept.-Oct.) 1935) concludes that accommodative asthenopia is an important *symptom* in this condition. The neuritis arises not only from a lesion of the optic nerve in the optic canal, but also in its course through the orbital fat,

**TUMORS.**—Tumor of the optic nerve in a child 3 years of age is reported by K. Schwarz (Arch. f. Ophth. 135: 247, 1936). The eye was proptosed 3 mm. Choked disc was present and some parts of the papilla appeared solid and gray. Grossly, the growth occupied the entire orbital portion of the optic nerve and extended through the cribriform fascia into the disc. Microscopically, it had the appearance of a mixed form of *endothelioma*.

**ORBIT.—NEOPLASMS.**—A. I. Pokrovskiy (Averbach Jubilee Volume, p. 352, 1935) describes as vascular tumors of the orbit, simple angioma, cavernous angioma, angiofibroma, massive retrobulbar hemorrhage in a hemophiliac and a hematoma which simulated a neoplasm in the walls and lumen of an ectatic lacrimal sac. Angiomas develop from embryonal rests of the vascular system. Although benign, they may become endotheliomatous and cause pressure atrophy of the optic nerve. **Early removal** is advisable.

**RESTORATION.—Plastic Surgery.**—G. E. Clay and J. M. Baird (J. A. M. A. 107: 1122 (Oct. 3) 1936)

describe a method for the restoration of the orbit and for the repair of defects of the conjunctiva by **grafts** taken from the **prepuce** or the **labia minora**. They have found that this tissue is ideal as a substitute for conjunctiva because of its availability and the appearance. This graft is pinkish, thin, hairless, possesses very little fat and does not have the objectionable features of the usual skin graft, *e.g.*, unsightliness, discomfort, desquamation and odor.

It is used for the correction of *symblepharon* and defects resulting from excisions of large growths from the *conjunctiva*. The graft is cut slightly larger than the size of the defect, and sutured in place with very fine silk. **Boric acid ointment** is introduced into the conjunctival sac and a patch is applied for 3 days. Sutures are removed on the fifth day and the patch on the seventh day.

A graft is obtained from the labia minora by making a quadrilateral incision within the vestibule between the inner margin of the labia minora and the edge of the hymen. Skin is obtained from the prepuce by circumcision. Two cases are reported. A conjunctival graft was made in one case and the socket was restored in the other.

Various methods of plastic surgery of the orbit and the eyelids are described by A. A. Kolen (Averbach Jubilee Volume, p. 209, 1935). He finds that horse-hair is the best suture material. Physiotherapy improved the postoperative result. In some cases, instead of restoring the conjunctival sac by plastic operation, he advocates forced stretching of the conjunctival sac by the introduction of the largest possible prosthesis and suturing the eyelids together for from 4 to 7 days. In other cases, instead of using a plastic compound, he lines the cavity with vaseline gauze and then packs it with packing gauze.

**RETINA.—CYSTS AND EPENDYMOMAS.**—In a discussion of cysts and ependymomas of the retina, C. Dejean (Arch. d'Ophth. 53:81 (Feb.) 1936) directs attention to (1) cysts of the retina which he considers a local reproduction of the primitive ependymal cavity; (2) tubular formations in the ciliary body which are produced by chronic inflammation characterized by a regressive metaplasia; (3) tumors of the infantile retina, neoplastic dysembryoma; (4) tumors of the adult retina. He also considers as dysembryoma, pigmented epithelioma of the iris and ciliary or cilioretinal epithelium. He classifies them as ependymomas.

**DETACHMENT.—Etiology.**—In a discussion of *hereditary* detachment of the retina, H. Richner (Arch. f. Ophth. 135:49, 1936) states that he observed detachment in 14 families in a single generation and in 18 families in successive generations, among 32 families with spontaneous detachment of the retina. These were not found as a rule in more than 2 generations. He concludes that a dominant type of inheritance seems to exist. In 41 individuals belonging to 22 families, myopia was associated with detachment.

According to K. Velhagen, Jr. (Klin. Monatsbl. f. Augenh. 96:26 (Jan.) 1936), *tuberculosis* or an unknown factor may cause detachment of the retina in juveniles in contradistinction to that which occurs in senile and myopic eyes of adults.

**Treatment.**—C. B. Walker (Am. J. Ophth. 19:558 (July) 1936) describes **surgical treatment** of separated retina by the **galvanic method**. He uses multiple galvanic micro-needle punctures, with  $\frac{3}{4}$  ma. negative current applied for 1 or 2 seconds. He recommends Vogt's technic with the following changes: The anode should not be applied to the sclera but kept as far away

as the diathermic pad on the shoulder; the galvanic voltage should be raised to 45; unipolar application should be made with fine, nonbreakable, iridium-platinum needle electrodes in preference to steel.

Excellent results were obtained in certain types of detachment. Others required **diathermy** instead or in addition.

A. Vogt (Klin. Monatsbl. f. Augenh. 96:10 (Jan.) 1936) recommends his method of **cathode electrolysis** for the treatment of detachment of the retina. During operation, orientation is facilitated by the development of a white foam. He obtained satisfactory vision in 2 cases of detachment resulting from cystoid holes in the macula.

A. von Szily and H. Machemer (*Ibid.* 96:191 (Feb.) 1936) recommend the use of **bipolar electrolysis** for the treatment of detachment of the retina. By closely approximating the two poles, the penetrating action of the current is limited to only a small portion of the eye. Of 40 operations, total reattachment was obtained in 18, improvement in 4, and no improvement in 9 (almost hopeless cases).

**FIBROSIS.**—A. B. Reese (Am. J. Ophth. 19:576 (July) 1936) describes massive fibrosis of the retina in children, a condition characterized by the presence of a grayish-white mass protruding from the retina which has the appearance of retinoblastoma.

Microscopic examination revealed that the mass was due to organization of hemorrhage which had occurred during delivery analogous to intracranial hemorrhages in the newborn. By contraction of fibrous tissue, the retina is drawn more and more into the lesion, so that the mass appears to be enlarging, which may lead to the faulty diagnosis of retinoblastoma.

In *children*, *hemorrhage* takes place in the external plexiform layer of the

retina, in which the retinal vessels terminate. Detachment of the retina is usually absent because fibrous-like plaques unite the lesion in the retina to the choroid. All the lesions are at the macula.

In *adults*, *hemorrhage* usually takes place from the larger vessels in the internal layers of the retina and spreads inward toward the vitreous. The hemorrhage may become absorbed or organized and produce detachment of the retina.

Other conditions due to organized hemorrhages in the retina are as follows: exudative retinitis of Coats, retinitis circinata, macular degeneration and disciform degeneration of Kuhnt-Junius, and metastatic ophthalmia.

Usually the retina is not detached because the lesion is adherent to the choroid.

**HOLES.**—*Localization.*—For the localization of holes in the retina, J. A. van Heuven (Brit. J. Ophth. 20:39 (Jan.) 1936) suggests the use of a curved glass rod (3 to 1.5 mm. in thickness) which has a flattened knob at its end, and a platinum wire running through it. The bar is silvered and varnished but the varnish is absent at the flattened knob. By means of a screw-tap, one end of the bar is made to fit an electric ophthalmoscope after Simon. The light of the ophthalmoscope is totally reflected by the silvered walls of the bar and finally is stored in the flattened knob out of which it is only allowed to escape through the small opening where the cover is scratched off. The rod is introduced under the conjunctiva and the sclera is transilluminated in the region of the tear in the retina. The two lights are made to coincide with the hole seen ophthalmoscopically. A diathermy current is passed through the platinum wire, so that a small spot is burned on the sclera

which serves to indicate the point at which the operation is to be performed.

**MACULAR DEGENERATION.**—R. I. Lloyd (Am. J. Ophth. 19:216 (Mar.) 1936) describes *hereditary* degeneration of the macula, exclusive of amaurotic family idiocy. He subdivides this condition into: (a) those with a number of white spots or dots throughout the periphery or about the macula; (b) those with early pigment changes in the macula (usually associated with poor vision); and (c) those that simulate partial coloboma of the choroid.

In the first type the macula is not involved, so that vision is good until late in life. There are a number of large white or yellowish spots about the macula. Another form of the first type is characterized by the presence of finer and much more numerous white spots. The macula may escape entirely, but it is usually ultimately affected. The spots appear first in the periphery, and night blindness is usually present. In a few cases these white spots are seen in the periphery of the fundus and symptoms are absent. Severe cases terminate in blindness, and some cases present black pigment corpuscles in the periphery which have the appearance of retinitis pigmentosa. The optic disc may become atrophic. These cases have been called *retinitis punctata albescens*.

In the second type, fine black pigment changes which resemble grains of snuff are seen in the macula. Vision decreases and a central scotoma may develop. The condition may remain stationary or may progress to tapetoretinal degeneration. Sclerosis of the choroidal vessels becomes visible. Central vision is lost and complete blindness may result in those cases in which these macular changes occur before puberty; mental deterioration usually results; if the disease occurs after puberty, however, the mentality is not involved.

The third type has the appearance of a partial coloboma of the choroid at the macula. The vision may be normal in one eye and fair or very poor in the other. The eyes are usually not affected simultaneously and the changes in the macula may not be visible until later in life.

#### **MACULAR DETACHMENT.**—

Three cases of idiopathic flat detachment of the macula are described by F. B. Walsh and L. L. Sloan (*Am. J. Ophth.* 19:195 (Mar.) 1936). This condition, which occurs most frequently in men between 30 and 45 years of age, arises from a localized separation of the retina rather than from a localized edema of the retina and adjacent choroid. It is characterized by sudden onset of diminished visual acuity, metamorphopsia, micropsia, a positive scotoma and hyperopia in those cases in which the fovea is involved. The scotoma, metamorphopsia and hyperopia disappear and the vision becomes normal after several months, but micropsia usually persists. Recurrences are common. Examination with the ordinary ophthalmoscope presents a change in the macula which has the appearance of early choroiditis. Examination with a binocular ophthalmoscope reveals a swelling in the region of the macula 3 to 4 disc diameters in area and a few small yellowish spots in the retina. They point out that flat detachment of the macula has been erroneously termed central chorioretinitis and central retinitis but its course and sequelæ are unlike those of central retinitis or central chorioretinitis.

Flat detachment at the macula is distinguished from: (a) circumscribed detachment due to tumor, which is usually accompanied by an increasing loss of vision and defect in the field of vision; (b) central choroiditis, which is accompanied by marked loss of vision; (c) retrobulbar neuritis, in which metamor-

phopsia, micropsia and temporary hyperopia are absent; (d) actinic retinitis, in which the symptoms and appearance may be similar but a history is given of exposure to heat or light; (e) syphilitic central recurrent retinitis, a rare condition, the appearance of which is the same. It is characterized by alternating loss of vision in both eyes lasting only a few days.

The most rational *treatment* is the **removal of foci of infection.**

#### **MACULA-HOLE.**—*Etiology.*—

H. V. Würdemann (*Am. J. Ophth.* 19:457 (June) 1936) reports a case of a hole in the macula which resulted from exposure to an electric welding light. A girl 16 years of age developed a *burn* of the macula from watching the welding performed with an electric torch at a distance of 4 to 6 feet. Vision became blurred shortly afterward. Ten days later, when first examined after this accident, vision was  $\frac{20}{200}$ , a central scotoma was present, and edema and hemorrhage of the macula were seen.

He points out that burns resulting from light and heat destroy the macula and that the macula is vulnerable to trauma, contusion, lightning, electric flashes, light, electric welding, direct sun, and observation of an eclipse.

At first tumefaction with or without hemorrhages develops at the macula. This is resorbed after 2 or more weeks so that the injury becomes visible with the ophthalmoscope. In slight injuries little or no degeneration is visible but in severe cases a true hole is seen.

**Treatment.**—In a discussion of the treatment of the flat type of detached retina and of hole in the macula by means of special devices and modifications, C. B. Walker (*Ibid.* 19:392 (May) 1936) recommends the use of noninsulated iridium-platinum micropins in the **diathermic treatment** of flat or shallow detachments of the retina. His

short-stop multiple micropins penetrate just to the choroid and when released by the forceps remain anchored in the sclera, so that loss of fluid is prevented until the pins are removed. For flat detachments, he advocates the use of a curved single pin and short-stop pin, both single and multiple.

He concludes as follows: Curved  $1\frac{1}{8}$  mm. single micropins are best for flat retinal detachments. The detachable four-prong short-stop pin is of assistance in those cases which present large areas of detachment and in which excessive leakage is desired. All pins in the sclera should be treated for 1 second with a 1 ma. negative galvanic current as a further aid to close unexpected retinal holes seen after micropuncture. After subscleral undermining to the back of the macular choroid, the injection of  $\frac{1}{50}$  c.c. of  $3\frac{1}{4}$  per cent. alkali with a special syringe and needle produces excellent results.

**LIPEMIA RETINALIS.**—J. H. Allen and W. A. Howard (Am. J. Ophth. 19:645 (Aug.) 1936) report a case of lipemia retinalis which occurred in a girl, 11 years of age, in diabetic coma. Her blood sugar was 335 mg. per cent., cholesterol 2454 mg. per cent., lipoid phosphorus 76 mg. per cent., and lecithin 1900 mg. per cent. Lipemia of the retina persisted for 3 days.

**RETINITIS.**—A. E. Edgerton (*Ibid.* 19:463 (June) 1936) reports a case of typical *circinate retinitis* in a woman, 51 years of age. He states that it is a painless progressive degeneration of unknown etiology. It is associated with a central scotoma and gradual loss of vision. White spots encircle the fovea more or less completely, are sharply defined, and often coalesce to form glistening patches. An area of normal-colored retina usually lies between the fovea and the circle. Retinal vessels pass over the white spots. Later, the spots char-

acteristic of *retinitis circinata* appear. He expresses the opinion that the condition is probably due to a toxin which affects the retinal vessels.

B. Samuels (*Ibid.* 19:493 (June) 1936) describes a condition in the retina which he calls *retinitis serosa* to correspond with postoperative or post-traumatic iritis serosa. He points out that the diseases are independent of each other.

He examined microscopic preparations of 59 eyeballs in which a diagnosis of iritis serosa had been made. In the retina a similar condition, "retinitis serosa," was found.

The iris was characteristically infiltrated with "lymphocytes and plasma cells." The retina (*retinitis serosa*) presented a remarkable parallelism with the iris (*iritis serosa*), *i. e.*, (a) cellular infiltration with lymphocytes and plasma cells mainly between the nerve fibers and the ganglion cells; (b) edema; (c) perivascularitis in addition to the general infiltration in the retina.

Retinitis serosa is a reaction separate from the reaction in the iris. Samuels concludes that irritating substances from disintegrating lens matter were the direct cause of the iritis and retinitis.

C. C. Charlin (Ann. d'ocul. 173:285 (Apr.) 1936) is of the opinion that *albuminuric retinitis* results from general intoxication by an abnormal intermediate product of protein metabolism. In some cases of albuminuric retinitis the retinitis improved or disappeared completely when a low protein diet was administered. However, in other cases renal insufficiency persisted and the patients died in coma.

G. Guist (Med. Klin. 32:350 (Mar. 13) 1936) regards *retinitis pigmentosa* as an endocrine disturbance with faulty metabolism of the mineral salt (chloride retention), and insufficient utilization of

oxygen (shallow respiration, lowered metabolism). They advocate a mixture of individually prepared **hormone** and pure **oxygen**, and doses of **renal lipoids** in cases of chloride retention.

N. K. Monyukova (Sovet. vestnik oftal. 8:348, 1936) explains that lysates stimulate the cell metabolism of the dying cells in *retinitis pigmentosa*. Fifty-eight per cent. of a series of 43 patients treated with injections of **tissue extracts of retina, liver, pituitary, adrenal cortex, and corpus luteum** showed temporary improvement of visual acuity, adaptation and fields.

I. Merkulov and R. Kopit (*Ibid.* 8:369, 1936) report that they obtained definite functional improvement of adaptation, visual acuity and fields in 13 cases of *retinitis pigmentosa* by treatment with **ocular and liver lysates**.

**RETINOBLASTOMA.—Diagnosis.**—R. L. Pfeiffer (Arch. Ophth.

15:811 (May) 1936) points out that an x-ray diagnosis of retinoblastoma can be made in 75 per cent. of cases. Calcareous degeneration produces a granular or mottled and irregular shadow which is roentgenographically pathognomonic of tumor when found in the eyes of children.

**RETINAL TEAR.**—C. B. Walker (Arch. Ophth. 15:1094 (June) 1936) describes a special instrument for *localization* of a retinal tear and its *treatment* by **galvanic current**. This device permits the passage of a 25 per cent. iridium-platinum micro-needle, the diameter of which is  $\frac{3}{1000}$  inch, through a 25-gauge stainless steel or platinum cannula, attached to a 2 c.c. hypodermic syringe. The instrument is fitted with a guide bar which can be adjusted to permit penetration to any desired depth. Two sharp spurs prevent slipping of the tip of the cannula.



# OTORHINOLARYNGOLOGY

Edited by FRANCIS L. LEDERER, M.D.

## DISEASES OF THE MOUTH AND LIPS

By A. R. HOLLENDER, M.D.

### CANCER OF LIP.—*Treatment.*

—Treatment of cancer of the lip by methods developed during the past 20 years at the Memorial Hospital is discussed by H. E. Martin (Am. J. Surg. 30:215 (Nov.) 1935). In early cancer of the lip, all of the accepted methods of treatment, such as surgery, radiation or cautery, if properly employed, have an equally good chance of permanent cure, provided that metastases to the neck have not occurred. Preference for radiation for the small primary lesions is based entirely on the superiority of the cosmetic result. The comparative merits of radiation and surgery in the treatment of cancer in general cannot be very convincingly proved by the results of either method in cancer of the lip. Histologic confirmation of the clinical diagnosis is essential in cancer of the lip, where curative treatment is intended either by surgery or radiation. In the advanced types of superficial lesions, contact application of filtered **radon** is used. Moderately advanced lesions of thickness up to 4-10 mm. should not be treated by contact application of radon alone. Such growths are best irradiated by a combination of contact application and the implantation of **radon gold seeds**. Operation may be refused in certain cases of bulky tumors of the lip, which as a general rule are best treated by surgery. If the patient will not submit to surgery, radiation is

the only other possible method of treatment, and adequate dosage can only be obtained by the use of interstitial radiation in the form of seeds or needles. When surgery is employed, **plastic repair** becomes essential. If the condition of the neck nodes warrants the attempt, the involved portions of the lip and cheek may be widely removed by cautery, and the skin and mucous membrane about the edges loosely approximated, leaving the defect wide open to be closed by a later plastic operation. The treatment of cervical metastases should be considered as a separate problem.

**CANCER OF MOUTH.**—A comprehensive and detailed study of carcinoma of the mouth has been made by H. L. Albright (Radiology 25:24 (July) 1935), who emphasizes especially the therapeutic aspect. At the outset it is pointed out that while intraoral cancer is among the most accessible, it remains the most fatal of malignant diseases. It has been shown that over 90 per cent. of malignant tumors of the mouth are epidermoid carcinomas, mostly of the adult resistant type. The "semi-malignant" or precancerous lesions, especially when diagnosed early, are curable. Enlarged cervical nodes should be regarded as cancerous, and results will depend on an early diagnosis more than any other single factor. **Radium** application in

accordance with the 1934 technic of the Radiumhemmet, Stockholm, and L'Institut du Radium, Paris, has proved to be the most effective treatment in all cases beyond simple operative removal. Intra-tumoral radium must be of epidermicidal intensity, whether over a short or long period, to be reliably effective. In this form it is the best caustic ever devised. In the treatment of the cervical lymphatic areas, irradiation is uncertain. It should be used only in combination with surgery, which should be early and radical. Better management of the individual case will result from the surgeon and radiologist working together rather than from either alone.

**ADENOCARCINOMA OF ORAL CAVITY.**—Adenocarcinoma of the oral cavity is uncommon and, probably, for this reason has received but little attention in the literature. W. L. Watson (Am. J. Roentgenol. 34: 53 (July) 1935) believes that these tumors form a definite group, with typical pathological and clinical characteristics which entitle them to a separate classification among the intraoral neoplasms. The author describes briefly the pathology and, in some detail, the clinical course of 41 cases of intraoral carcinoma admitted to Memorial Hospital in the past 15 years. He states that these tumors are in the majority of instances derived from the minor salivary glands of the oral cavity, but may rise from aberrant thyroid tissue or from mucous glands. The micropathology is only fairly constant, but the gross appearance of these tumors is diagnostic. Clinically, these tumors have a marked tendency to local recurrence, bone invasion, and widespread metastasis by way of the blood or lymph stream. The radiosensitivity of these growths could not be definitely forecast by the microscopic picture, but clinically, with one or two exceptions,

this group was quite radioresistant. Present treatment is by a combination of external and interstitial **irradiation** followed by **cautery excision**. The *prognosis* is poor.

**ORAL MANIFESTATIONS OF BISMUTH.**—That local oral hygiene and tartar deposits are responsible for the high incidence (80 per cent.) of bismuth pigmentation in the mouth is stressed by F. P. McCarthy and S. O. Dexter, Jr. (New England J. Med. 213: 345 (Aug. 22) 1935). The contact buccal mucosal pigmentation is shown to be definitely due to irritation from the opposing gingival irritant, which is essentially tartar. Severe cases of gingival pigmentation and inflammatory reaction are relatively few, and for about 10 years since the preparation of insoluble bismuth salicylate in oil has been in use, the number of cases of necrosis and gangrene has been extremely rare. Therefore, this drug may be considered a safe therapeutic agent in the treatment of syphilis, as the presence of pigmentation and mild gingivitis seems to have no deleterious effect on the general health of the patient. Nephritis was absent in all but a few isolated cases. Blood dyscrasia related to bismuth therapy was likewise absent. In contrast to the hospital cases studied in this series, a small control group of office patients under bismuth salicylate therapy showed a low incidence of pigmentation, about 5 per cent.

**STOMATITIS.**—*Etiology.*—It is not generally recognized either by physicians or by dentists that an irritant stomatitis may result in a susceptible person from sensitization to materials in dental plates, particularly the newer synthetic substitute for rubber plates. Three such cases have been observed by

H. Rattner (J. A. M. A. 106:2230 (June 27) 1936). The processes used in the manufacture of the various synthetic base plates are trade secrets, but, judging from what is known about them, it is quite likely that at some step in the process a compound is formed or an ingredient is used which might be irritating to the tissues in the mouth of a susceptible person. The cases here-

with reported would seem to indicate so, for in none of them could the symptoms be accounted for on the basis of mechanical faults, infections, or other medical factors, and, so far as could be determined, irritants such as dentifrices could also be eliminated as etiologic agents. In 2 of the cases reported, there were strong reactions to patch tests on the skin made with the denture material.

## DISEASES OF THE PHARYNX AND TONSILS

By A. R. HOLLENDER, M.D.

**PHARYNX. — GRANULOCYTIC ANGINA.**—The subject of granulocytic angina, a term preferred by I. Frank (Arch. Otolaryng. 23:310 (Mar.) 1936) because of its more accurate designation of the characteristic blood picture, is reviewed with a report of 3 cases, 2 terminating fatally. Granulocytopenia may be caused by a number of agents, among which the drugs of the coal tar derivative series, if used continuously, may be included. A sore, ulcerated mouth and throat are frequently the result of granulocytopenia. The presence of throat symptoms with the characteristic blood picture of granulocytopenia verifies the diagnosis of granulocytic angina. If there is a continuous use of drugs of the coal tar series, this should suggest a rational cause for the condition.

**Treatment.**—The rational treatment is to remove the cause and to stimulate the hematopoietic system. The use of all coal tar drugs or others capable of producing leukopenia should be discontinued. **Pentnucleotide** injected intramuscularly or intravenously, or administered, well diluted with 100 c.c. (3½ ounces) of **physiologic solution of sodium chloride**, by the continuous drip method, offers at the present time one of the best methods of stimulating

the bone-marrow, and more satisfactory results have been reported from its use than following the administration of any other remedy. The dose is usually from 10 to 22 c.c. (2½ to 4½ drams), repeated twice daily. A favorable response may be expected about the fifth day. Attention is called also to the use of **adenine sulphate**, **x-rays** and **liver extract**. Frank states that under early treatment the mortality in cases of granulocytic angina has fallen to less than 30 per cent.

Attention is called by H. N. Tihen (J. Kansas M. Soc. 37:142 (Apr.) 1936) to the earlier use of **liver extract** parenterally as a major therapeutic measure in the treatment of agranulocytosis. In his opinion, the preponderance of evidence at present points to agranulocytosis as a syndrome of defective function of the bone-marrow, especially of its leukopoietic function, probably produced by several known and unknown etiologic factors. A stimulation of the leukopoietic function, as well as of the other functions of the bone-marrow, by liver and its extracts, has been demonstrated by various observers since the introduction of liver as a therapeutic agent in pernicious anemia. In the majority of cases which have been unsuccessful in their progress, the author

contends that inadequate liver dosage was used, although he realizes that probably in some of the very acute fulminating cases the damage to the bone-marrow is so severe that no remedy will be of avail. When, however, liver was used in adequate amounts, it has produced the most satisfactory results yet reported. The recent increased concentration of liver extract, 1 c.c. equivalent to 100 grains of fresh liver, makes the parenteral administration of large doses easy. A case is reported of a patient who responded rapidly through the use of heavy doses of liver extract intramuscularly. The essential treatment consisted of heavy dosage of liver extract intramuscularly, 1 c.c. (equivalent to 100 Gm. of fresh liver) every 3 hours, day and night, beginning as soon as the patient entered the hospital. In 3 days, this was reduced to every 4 hours; in 5 days, to twice daily, and in 10 days, was replaced by liver extract by mouth (9 capsules of **extralin** daily).

**LEUKEMIA.**—*Diagnosis.*—A. A. Love (Arch. Otolaryng. 23: 173 (Feb.) 1936) has rendered a complete report of the manifestations of leukemia encountered in otolaryngologic and stomatologic practice. He believes that leukemic lesions are frequently misdiagnosed or their complete significance is entirely overlooked. In the ear the disease may be present as otitis externa, with formation of hemorrhagic blebs in the canal and on the drum membrane. In the nose, the most frequent manifestation is epistaxis. In the oral cavity, the pathologic changes are most varied. In some cases there are pale gums of normal contour, and in others, hypertrophied, spongy gums that bleed at the slightest touch and resemble those with scurvy. In some cases, the gums simulate typical Vincent's angina, with consequent soreness and bleeding; in others, there is actual necrosis of the tissue of the gums,

which does not simulate any usual dental infection. On the surfaces of the mucous membranes of the upper respiratory tract, especially in the mouth, the throat and the larynx, there are in some cases multiple hemorrhagic blebs. These break down rapidly and form necrotic areas, caused by invading organisms. At times there is an area of necrosis on the cheeks or lips. In the throat, the necrotic lesions appear usually on the tonsils. In the larynx, the necrotic areas may extend downward from the region of the posterior molars or tonsil or may be initiated in the laryngeal structures themselves, usually owing to a breaking down of a hemorrhagic formation of blebs on the mucous membrane. In a comparatively few cases, leukemia is first manifested by enlargement of the glands of the neck. The appearance of any of these symptoms without obvious cause points to the possibility that the patient may be suffering from a blood dyscrasia, especially a form of leukemia. These findings, together with the other general symptoms of this type of disease, indicate the need of an accurate hematologic study.

#### **GRANULAR PHARYNGITIS.**

*Treatment.*—The clinical significance of compensatory granular pharyngitis is stressed by H. I. Lillie (Arch. Otolaryng. 24: 319 (Sept.) 1936), who is firmly convinced that the most frequent cause of pharyngeal complaints for which patients seek advice is referable to the pharynx itself. The symptoms are numerous and varied. Clinically it is often possible to anticipate the occurrence of pharyngeal symptoms after the removal of infected tonsils and adenoids of children, or the faucial tonsils of adolescent boys and girls or adults. The inclusive and descriptive term of "lymphatism" may well be chosen for this particular group of patients. The treatment has consisted of x-rays, drugs,

gargles and sprays. **Diathermy coagulation** has been used to eliminate certain definite follicles and enlargement of lateral pharyngeal bands. While this causes a definite objective change, it usually does not eliminate the symptoms. Surgical removal of the lateral pharyngeal band or the numerous follicles on the pharynx is difficult and usually results in hypertrophy and hyperplasia of the remaining follicles. The application of chemical caustics, especially **silver nitrate** in solutions of various strengths, has long been a favorite method of treatment. It may relieve the symptoms temporarily by producing coagulation of the surface epithelium or mild scarring. In some cases, however, the patient himself has used silver nitrate to the point where general argyria has developed.

The author advocates **general treatment** for the relief of granular pharyngitis, appreciating that such treatment has been carried out in the past on an empirical basis. **Syrup of hydriodic acid** or some such preparation has been used, and in certain instances beneficial results have been obtained, particularly in the case of children. At present, iodides by mouth in some such convenient form as **ethyl diiodobrassidate** over a period is preferred. The preparation comes in tablet form, it is palatable and apparently the organic composition is such that the unpleasant symptoms associated with the ingestion of iodine are to a large extent eliminated. The tablets are chewed and swallowed. Depending on the degree of involvement, 1 tablet is given from 2 to 4 times a day for a period of 5 days, the amount being lessened as the symptoms ameliorate. This drug may be given to children, although **syrup of hydriodic acid** seems to have a similar effect if given over a period of time. This method of treatment has given patients more relief and caused more definite changes

in the appearance of the pharynx than any other remedy that has yet been used.

**Irradiation** of lymphoid hypertrophies and infections of the pharynx and nasopharynx is advocated by W. W. Eagle and R. J. Reeves (Southern M. J. 29: 159 (Feb.) 1936), as a result of their studies and those of Soto. The authors stress in particular the nonencapsulated lymphoid tissue which is found scattered over the pharynx and nasopharynx, especially that tissue which cannot be surgically removed with any degree of satisfaction. Persistent or recurrent infection of this tissue and systemic disorders have been observed which make it obvious that the lymphoid tissue in the pharynx should, by all means, be thoroughly eradicated. Treatment by irradiation was carried out in 143 patients of whom 67 have reported the results thus far obtained. In 47 of the latter (70 per cent.) good results were obtained, in 16 (24 per cent.) the results were questionable, and in 4 (6 per cent.) the results were poor.

The technic of irradiation in these cases has been standardized during the last few years. The dosage was carried out under the following conditions: 130 K. V., 5 ma. 25 cm. distance and 3 mm. aluminum filter. The erythema dose using these factors is 375 r units. The dosage first used was 100 r administered over each side of the neck at weekly intervals, giving 4 to 6 treatments in a series. This dosage in some patients produced considerable dryness of the nasopharynx; therefore, the treatments, where possible, were given at 2-week intervals, using 150 r as the dosage over each side of the neck. The immediate reaction depended on the degree of infection of the lymphoid tissue. This reaction was characterized by a congestion and swelling, and often, 4 to 6 hours after the treatment, the salivary glands and cervical lymph nodes be-

came enlarged. This reaction of lymphoid tissue to x-ray irradiation has been fully discussed by Akaiwa in his recent article and also by Soto in 1932.

The authors do not always expect to find an obvious total destruction of large lymphoid follicles, but the diameter does decrease in size, leaving only the stroma, following the total dosage administered. The small follicles and the granular-looking pharynx, however, do lose their original appearance.

**LUDWIG'S ANGINA.**—*Treatment.*—R. P. Gingrass (Wisconsin M. J. 34:905 (Dec.) 1935) states that Ludwig's angina is an acute, rapidly spreading infection of the cellular planes, starting in the floor of the mouth and extending to the front of the neck.

The author holds with Blair and others that it is as definite in its pathology and clinical signs as pneumonia and peritonitis. Ludwig's angina is credited with a mortality of 40 per cent. or higher. With the method of treatment described, the mortality rate is practically zero.

The treatment is essentially early free incision under **ethylene** or **nitrous oxide anesthesia**. A median incision is made extending from the lower border of the mandible to the hyoid bone. The incision is carried down to the mylohyoid muscle. This muscle is split in the midline and a small hemostat inserted between it and the geniohyoid muscle and then spread open. Entrance to the floor of the mouth is thus obtained. This is followed by a large hemostat which is carried upward, backward and outward. The hemostat is now above the mylohyoid muscle and medial to the internal surface of the body of the mandible; in other words, it is in the floor of the mouth. The hemostat is opened and then withdrawn. The same procedure is repeated on the opposite side. A small fenestrated rubber tube is inserted into

each opening. They are removed in about 24 hours. Frank pus is rarely seen at the time of establishing drainage. The following day a rather dark-colored, thin fluid may be seen around the incision and tubes. By the second day, foul smelling pus appears. **Hot magnesium sulphate dressings** are applied to the neck every hour. General supportive treatment is given. The patient's pain is controlled by anodynes. A semi-recumbent position is maintained. Tracheotomy should be reserved for difficult respiration. Posture during sleep is a factor in avoiding or lessening aspiration-pneumonia.

Where the swelling is more one-sided, in addition to making the median incision and establishing drainage up into the floor of the mouth, a transverse incision is made extending from the lower part of the median incision backward over the anterior belly of the digastric muscle. A hemostat is carried upward and backward toward the submaxillary salivary gland. Occasionally, a suppurating lymph node will be encountered. A drainage tube is then inserted. This procedure may be repeated on both sides if necessary, variation from the treatment described may be called for. When the induration is entirely above the mylohyoid muscle, intraoral incision is usually sufficient, but when the induration involves the floor of the mouth and the front of the neck, a typical Ludwig's angina, the treatment recommended should be carried out. In the opinion of the author, many lives will thus be saved, whereas procrastination leads to a fatal outcome.

#### **PHARYNGOGENIC HEMATOGENOUS STREPTOCOCCIC PERITONITIS.**

—Sore throat of the streptococcic variety as a definite antecedent history in streptococcic peritonitis was brought to the attention by J. Felsen and A. G. Osofsky (Arch. Surg. 31:

437 (Sept.) 1935), whose studies covered 8 cases. The average period that elapsed between the angina and the onset of acute abdominal symptoms was 5.8 days. The average duration of the disease from the time abdominal symptoms were noted until death was 4.7 days. Extremely high temperatures were recorded (from 107° to 107.8° F—41.6° to 42.1°C). The pathologic picture in each case was essentially that of streptococcic septicemia with profound toxic effects. The histopathologic pictures in general were congestive or hemorrhagic, owing to a toxic effect on the walls of the smaller vessels. In most of the reported cases a hemolytic streptococcus was isolated. The authors believe that their group is exceptional, since 5 cases were of the viridans and 3 of the non-hemolytic type. The mortality was 100 per cent. In the experimental work, the disease was reproduced in most of the animals by the intravenous injection of 18-hour broth cultures. The ease with which they did this, even with some old cultures, suggests the possibility of a selective affinity of their strains for the intestine and peritoneum.

**TUMORS.**—*Carcinoma of the pharynx and larynx* with especial reference to treatment is considered by L. H. Garland (Radiology 24:261 (Mar.) 1935), who holds that many cases of malignant disease of the larynx and pharynx can be arrested and apparently cured by adequate, carefully administered, x-ray therapy. None of the present series of cases has been observed for a period of 5 years and, therefore, the number of "clinical cures" cannot be stated. It is pointed out, however, that 12 of 24 cases showed primary healing, and 7 of 24 cases are clinically arrested at the time of making this report (2 months to 1½ years), and that some of the other cases received remarkable palliation. No patients died from causes

directly attributable to the x-ray therapy in this series of cases. No late necroses of cartilage or bone, and no laryngeal or pharyngeal obstructions due to radiation were observed.

The treatment of *cancer of the mouth, pharynx and larynx* is reviewed with a report on several hundred cases managed by radiation methods. In the opinion of J. M. Martin (South. M. J. 29:221 (Mar.) 1936), radiation for cancers in these regions has passed the experimental stage. With better radium facilities and an improved x-ray technic, there is greater optimism for improved statistics in cancer on the inside of the mouth. Good cosmetic and functional results were obtained in cancer of the tongue. Coutard reported 20 per cent. of 5-year cures resulting from the use of his x-ray technic in the treatment of 212 cases of cancer of the pharynx and larynx. Radiation has become the method of choice for this region. Although the author's experience covers a period of only a little over 2 years, he is impressed with the wonderful possibilities of this method.

In presenting a study of 24 cases of *malignant tumors of the nasopharynx*, S. Salinger and S. J. Pearlman (Arch. Otolaryng. 23:149 (Feb.) 1936) emphasize particularly the histopathology and attempt to clarify the nomenclature of a type of growth which they believe is characteristic of this location. In examining most of the available reports they find that the tumors, roughly speaking, fall within 3 groups, *viz.*, carcinomas, sarcomas and endotheliomas. As a result of their study, these authors conclude that transitional cell carcinoma is the most common type (75 per cent.). In 3 cases, the diagnosis of sarcoma was considered, but in only 1 of these was there complete agreement. Lympho-epithelioma was diagnosed in 6 cases. Its similarity to transitional cell carcinoma

was noted in several cases, the difficulty of differentiating these growths being attributed to inadequate fixing and staining. Endothelioma was considered but not definitely agreed upon by pathologic study. The early and characteristic symptoms of transitional cell carcinoma were found to be: painless cervical adenopathy, tinnitus or deafness, and pains due to involvement of the first and second branches of the trifacial nerve. In the majority of cases, the tumor originated in the region of the Eustachian tube of the lateral wall of the nasopharynx, thus accounting for the symptoms enumerated.

The *treatment* consists in external irradiation of the involved tissues by means of the **x-rays** or **radium** packs, combined in some instances with surface application of radium to the local lesion. Whether x-rays or radium packs are employed, the underlying principle of treatment is that of the technic established by Coutard. The primary lesion and the regional lymphatic areas are exposed daily, or twice daily, to x-rays or radium over periods varying between 20 and 60 days. Adequate filtration is utilized to obtain the most highly penetrating rays. The total dose administered is estimated on a biologic basis, the aim being to cause complete regression of the growth without permanent damage to the surrounding normal structures. When the primary lesion is small and localized, surface applications of radium are combined with external radiation.

The choice between high voltage x-rays and radium packs cannot be stated with certainty at the present time. The 5-year results from the use of the former are now well established. Whether or not the use of the penetrating gamma rays of radium will improve these results remains for the future to determine. With rare exceptions, the total dose of radiation does not vary with the estimated

radio-sensitivity of the tumor. As a rule, the maximum dose compatible with the integrity of the tumor's bed is administered.

**SPOROTRICHOSIS.**—G. M. Loewe (J. A. M. A. 107:1040 (Sept. 26) 1936) reported a case of sporotrichosis of the cervical area which had baffled more than 50 consultants. The case presents several possibilities:

1. The original acute pharyngeal infection with secondary involvement of the cervical lymph node may have been due to *Sporothrix*. No local lesions, however, developed in the throat, and the teeth were found to be normal by direct and x-ray examination.

2. The primary infection of the pharynx and cervical node may have been due to a pyogenic organism, with later localization of the *Sporothrix* in the damaged node.

3. The process may have been a suppurative one until drainage to the exterior was established, with entry of the *Sporothrix* through the external sinus.

The duration of this condition was more than 2 years. Many forms of therapy were advocated: radical **excision** of the affected area was advised by 3 competent consultants. The orthodox therapy of iodides for sporotrichosis was ineffective. **Specific autogenous vaccines** were apparently effective and produced a marked improvement in the local condition. The residual lesion responded to **phenylmercuric nitrate** and dilute solution of **sodium hypochlorite**. The patient has remained cured for more than 15 months. The importance of proper bacteriologic investigation of chronic suppurative lesions is strikingly illustrated by the history of this case.

**TONSILS.—TONSILLECTOMY.**  
—*Technic.*—*Premedication and inhalation anesthesia* for tonsil and adenoid



operations is discussed by J. T. Gwathmey (Am. J. Surg. 31:272 (Feb.) 1936), who believes that premedication ensures a smooth induction of the anesthesia which is at all times under perfect control. The field of operation is dry and clear, and postoperative contingencies and complications are eliminated. The basis for the technic presented rests on laboratory experimentation and clinical experience. It is desirable to give the child a **sodium bicarbonate enema** on admission and 30 or 40 minutes before operation, with the patient in bed. **pentobarbital sodium** dissolved in 1 ounce of water is given by mouth, or rectally in 4 c.c. of cold water, if swallowing is difficult. The dose varies according to the age, size and condition of the patient. Generally, in children up to 7 years of age,  $1\frac{1}{2}$  grains (0.1 Gm.) of the drug is given; from 7 to 10 years, 2 grains (0.13 Gm.); more than 10 years of age, 3 grains (0.2 Gm.). For adolescents the dose of the barbiturate is preferably increased, or a suitable amount of a **morphine** derivative may be added. More than 90 per cent. of the author's patients are asleep within 15 minutes. With care in lifting the patient from the bed to the stretcher, he reaches the operating-room asleep. When time is essential, the operation may be performed while the patient is on the stretcher.

*Electrocoagulation.*—The present status of electrocoagulation of tonsils is surveyed by L. Savitt (Illinois M. J. 69: 127 (Feb.) 1936), who first reviewed the literature and then formed certain opinions concerning this method of tonsil removal. That tonsils can be completely removed by electrosurgery is supported by the reports of many workers. That the procedure is, however, indicated only in selected cases is now generally conceded. The limitations and contraindications are sufficiently well-

defined for appreciation of practitioners generally. In the author's experience, the method holds out as its main usefulness the destruction of tonsillar stumps and recurrent lymphoid tissue. It is pointed out that in children and nervous individuals the procedure cannot be successfully carried out. The consensus of opinion is that surgery will continue to be the method of choice for the removal of tonsils. Since there is some value to the procedure in special and selected cases, the laryngologist should familiarize himself with its technic that he may not be limited by a lack of knowledge in its application when the indication warrants.

*Effect of Tonsillectomy on Incidence of Rheumatism in Children.*—

The influence of tonsils on rheumatic infection in children was studied in a very large series of cases by A. D. Kaiser (J. Lab. and Clin. Med. 21:609 (Mar.) 1936). Based on data obtained from the parents, nearly all the rheumatic manifestations occurred less commonly among tonsillectomized children. Rheumatic fever, which is usually a severe type of rheumatic infection, was reported with considerably less frequency in tonsillectomized children. Among the tonsillectomized children there were 37 per cent. fewer cases of rheumatic fever. Muscular rheumatism, termed growing pains, was reported only slightly less often in tonsillectomized children. Chorea was noted with equal frequency in the two groups, while rheumatic carditis was somewhat less common among the tonsillectomized children. The statistical information based on the parent's history of the child leaves some uncertainty as to the value of the data. It does, however, clearly indicate that rheumatic disease occurs in children whose tonsils have been removed, and it also seems highly probable that initial attacks of rheumatic

infection are somewhat less likely to develop in children whose tonsils have been removed. Recurrent attacks of rheumatism occurred as frequently in tonsillectomized children as in the untreated ones at all ages, except between the ages of 10 and 15, when recurrent attacks are less common in both groups. Though the number of recurrences of such manifestations as rheumatic fever, chorea and muscular pains was not lessened by removal of the tonsils, it was demonstrated that carditis associated with recurrent attacks of rheumatic fever and chorea was somewhat less severe in the tonsillectomized children. Though the removal of the tonsils fails to decrease the number of recurrences of rheumatic infections, there is a decidedly lower mortality rate among these children. If other studies show similar results, there is a definite indication in every rheumatic child for the removal of the tonsils.

**Effect on Tuberculosis.**—That tonsillectomy in the tuberculous is followed by the same degree of general improvement as in the nontuberculous patients is emphasized by S. Broadwell (Illinois M. J. 68:526 (Dec.) 1935). Thus, in spite of the fear which has long prevailed of increasing the tuberculous activity; of producing an acute local lesion at the site of operation; of lowering the resistance through hemorrhage; of dysphagia. According to the author, there is just as definite an indication for the removal of infected tonsils in pulmonary tuberculosis, both active and quiescent, as there is for the removal of focal infection elsewhere. Active pulmonary tuberculosis should not be considered a contraindication for tonsillectomy when the operation is indicated. In selecting his cases the author excluded patients who were septic or in a hopelessly advanced stage. Broadwell's report is based upon tonsillectomies in 118 per-

sons, 70 per cent. of whom showed improvement in general condition, gain in weight, 1, 3 and 6 months after operation. Of this group, 6 positive sputums became negative and remained so. In 20 per cent., the active tuberculous condition was unchanged.

#### **CHRONIC TONSILLITIS.**—

Twenty-five consecutive cases in which a clinical diagnosis of chronic tonsillitis had been given were studied from a clinical, bacteriologic and pathologic standpoint by T. N. Hunnicutt, Jr., H. J. Sternstein and H. E. MacMahon (Arch. Otolaryng. 22:744 (Dec.) 1935). It has been shown that from the clinical aspect a single or group of changes was not found in all the tonsils and that the clinical findings did not bear a constant relationship to the clinical history. From a bacteriologic standpoint, one type of flora was not observed constantly in the tonsils, nor was any characteristic type of flora found showing a relationship either to the gross appearance of the tonsil or to the clinical signs and symptoms. From the standpoint of pathology, the changes in the tonsil, though variable, were strikingly similar to those in a group of selected controls. The histologic changes, with the rare exception of the specific lesion of rheumatic fever, did not bear a definite relationship to the bacterial flora or to the clinical signs and symptoms.

#### **HYPERTROPHY.—Treatment.**—

The treatment of hypertrophied tonsils, with or without recurring tonsillitis, by x-rays is discussed by A. Gentili. Progress was noted 1 month, 6 months, and 1 year after treatment. No subjective or objective disturbance was observed. In 4 cases, complete aplasia of the tonsils resulted; in 5, no effect was obtained; in the remainder of the series of 35 cases, the shrinkage was only slight, and in the majority only of a temporary character. Of the total of 35 children,

surgical removal of the tonsils had to be resorted to subsequently in 12 cases. Histologic examination of the excised tonsils showed a regression of the lymphatic tissue and proliferation of connective tissue. The x-rays produced greater reduction of infected than of noninfected hypertrophied tonsils.

**TUMORS.**—According to H. Jackson, Jr., F. Parker, Jr. and A. M. Brues (Am. J. M. Sc. 191:1 (Jan.) 1936), *malignant lymphoma* of the tonsil occurs with sufficient frequency to merit careful attention and study, particularly as it is likely to run a rapid and fatal course. In 15 years there were admitted to the Huntington Hospital, 236 cases of malignant disease of the tonsil. Of these 28 (11.8 per cent.) were proven to be malignant lymphoma of one type or another. Generalized lymphoma developed in 56 per cent. of this number. While the immediate response to radiation is excellent, it is by no means an index of the ultimate outcome. Local recurrence is common but, in 44 per cent. of those who died, there was no spread beyond the pharynx, nasopharynx and cervical nodes. The absence of local lymph nodes at the time of treatment is, in general, of good prognostic import. Lymphoma of the tonsil should be regarded as but one type of malignant lymphoma, and the ultimate widespread involvement seen in many patients must constantly be borne in mind. It is suggested that those patients be treated as if they had carcinoma of the tonsil, *i. e.*, with very heavy

initial radiation with comparable doses for recurrences.

**Treatment.**—Tonsillar cancer is managed best by radium therapy, according to P. Kisfaludy (Strahlentherapie 55: 429 (Mar. 21) 1936), who holds, however, that the larding with radium needles should be done by an experienced radiologist who has surgical knowledge. Kisfaludy employs needles containing 3.3 or 6.6 mg. of radium element.

Depending on the size of the tumor, from 4 to 10 needles are introduced and left in place for from 24 to 36 hours. He maintains that this method of application is superior to the former practice of using needles that contain only 1 to 2 mg., and that have to remain in the tissues for from 5 to 11 days. The shorter duration of the radium application reduces the secondary irradiation, the danger of tissue necrosis, of abscess and edema formation, and of general infection or hemorrhage. Moreover, it is less annoying to the patient if the radium larding remains in place only for from 24 to 36 hours instead of for a number of days. The regional glands are treated with x-rays; 200 r are applied from 6 to 8 times. After 6 or 8 weeks, the x-ray irradiations of the glands are repeated. However, if the glands are enlarged, they are excised and the surgical treatment is followed by irradiation. The results obtained with this combination method prove the advantage of the author's method of larding with radium needles.

## DISEASES OF THE NOSE AND SINUSES

By PHILIP A. HALPER, B.S., M.D.

### NASAL HEMORRHAGE.—

**Treatment.**—Severe nasal bleeding is a problem which confronts the rhinologist constantly, and it is especially distracting

when no visible source of the bleeding is apparent. The blood picture in these patients is usually within normal limits which indicate that the condition is en-

tirely local. Though the hemorrhage can often be seen coming from the anterior inferior part of the septum, cauterization with chemicals or the electric cautery does not always lead to permanent destruction of the offending blood-vessels, and recurrences are common. Radium, submucous resection, and the injection of sclerosing solution must be resorted to at times. Moccasin snake (*Ancistrodon piscivorus*) venom has been used as a therapeutic procedure in controlling hemorrhage. J. L. Goldman (Arch. Otolaryng. 24:59 (July) 1936) illustrates the beneficial effect of **moccasin snake venom** in the treatment of recurrent epistaxis. The most favorable results were obtained in those with the so-called functional bleeding abnormalities, idiopathic nasal bleeding which was not associated with any blood dyscrasia. The venom was diluted to 1:3000 with an 0.85 per cent. saline solution and preserved with a 1:10,000 dilution of sodium merthiolate. The initial dose was 0.5 c.c. (8 minims) of the 1:3000 dilution. Subsequent injections were rapidly increased to 1 c.c. (16 minims) as a maximum dose. For children, the initial dose was 0.3 c.c. (5 minims), 0.8 c.c. (13 minims) being the maximum amount. The patients in this series were given injections twice a week for variable periods, depending on the symptoms. If the nasal bleeding was not entirely controlled after 4 to 8 injections, 2 injections a week were continued until the clinical result warranted cessation of the treatment. There is no contraindication for more frequent injections of the venom when desirable.

Patients could be grouped according to the source of bleeding. The following classification was formulated: (1) telangiectasia of the nasal septum, (2) ulceration of the nasal septum, (3) bleeding without a visible source, and (4) hemangioma of the nasal septum.

The observations appear to substantiate the conception that the venom exerts its therapeutic effect by acting on the capillaries and on the smaller blood-vessels. For the proper evaluation of the snake venom therapy, the patients were exposed only to this form of treatment. In the regular course of recurrent epistaxis, it is expected that sinus infections will be treated, deviated septums corrected when necessary, and obvious bleeding points cauterized. The snake venom is offered as an additional and valuable therapeutic agent for the treatment of persistent and troublesome recurrent epistaxis. In the series which the author studied, the venom therapy was effective in practically all instances, either in completely arresting and controlling the nasal bleeding or in markedly diminishing its amount and frequency.

R. Wilenius (Finska läk.-sällsk. handl. 77:291 (May) 1935) reports a case of recurring nosebleed with multiple telangiectases and hemangiomas (hereditary hemorrhagic angiomatosis (Osler) in a woman, aged 58. In spite of the tendency to bleeding, no changes in the blood were demonstrable other than a secondary anemia due to the hemorrhages. A heredofamilial disposition to hemorrhages of simple dominant was established in 3 generations. The epigastric pains with melena in this case are ascribed to angiomas in the pyloric region. In early adult life, cauterization of the telangiectases in the nose was ineffective, but recent **cauterization together with general building-up treatment** resulted in marked improvement.

**NASAL FRACTURE.**—*Treatment.*—According to J. Poult (Schweiz. med. Wchnschr. 65:638 (July 13) 1935), the **reposition** of the fractures of the nasal cartilage can be accomplished readily by pressure with the

fingers from both sides and, if necessary, with simultaneous hook traction that has its point of attack in the concavities of the anterior portion of the nose. The traction is accomplished best with a blunt double hook that has an inner span of from 5 to 10 mm. The tips of the hook should be padded with cotton. If a fracture of the bony portions of the nose has to be reduced, a wide arterial forceps, that is kept closed, can be introduced along the nasal floor until the fracture has been reached. The eventually overlapping fragments are then loosened by traction with the double hook. If the vomer also is fractured, it can usually be replaced by traction. Finally, the depression can be lifted from the inside either by opening the forceps or by pressing the closed forceps flat against the depression. In order to retain the fragments in the proper position, the author employs an **intranasal support** that is made of glass and has the form of a triangle (musical instrument). To guard against asymmetry of the nose, he inserts the support into both nasal cavities, regardless of whether both are injured or not. The nasal support consists of a thick-walled glass tube with an external diameter of 5 mm. Each side of the triangle is about 3 cm. in length, and the middle piece measures about 1.33 cm. The inner distance between the two ends is about 3 mm. It is advisable to have a hole in one of the arms of the triangle and to lead a string through this and the tubal opening and knot it above the upper lip, so as to prevent the triangle from slipping backward. The author states that this supporting apparatus is well tolerated by the patients. It is worn for from 8 to 14 days. It permits the discharge of the secretions and in some instances even limited nasal breathing. The author considers that unless irrigation seems absolutely

necessary, it may be omitted, for, with the glass support, danger of stasis of the secretion is not great.

In discussing fractures of nasal and malar bones, G. B. New (S. Clin. North America 15:1241 (Oct.) 1935) states that **lacerations about the nose should receive the first attention**. The wound is cleaned with an antiseptic, and the bleeding is controlled. The skin is closed with eyeless needles and fine silk. The fractured parts are placed in position (manipulation under gas anesthesia). **Intranasal splints** are made by vaseline packs. Occasionally, **suture** may be necessary to hold the bridge in position. Outside, **aluminum splint** lined with a layer of gauze is used. Gauze and tape hold the splint in position. An **ice-bag** is employed outside this dressing. If the patient is unconscious and the bone driven back, the treatment is expectant. In old fractures, correction may require refracture.

The management of recent fractures of the nose and sinuses is well described by F. D. Woodward (Ann. Otol., Rhin. and Laryng. 44:264 (Mar.) 1935). He points out that fracture of the frontal bone involving the sinus is dangerous because of the relationship of the sinus of the brain and the meninges. The important thing to ascertain is whether the posterior wall is involved, because, if so, wide exposure, inspection of the dura and open drainage are required. In any case, blood clots and fragments of bone should always be removed. In fracture of both the ethmoid and of the frontal bone, the patient should be cautioned against blowing the nose. A *transverse fracture through the ethmoid bone and the orbit* is treated by **wiring** or by **dental braces fixed to a skull cap**. In fracture of the *maxilla*, blood is commonly found in the maxillary sinus. Irrigation should be delayed at least from

4 to 6 days because of the danger of secondary infection. It is always important to restore the orbital rim. The author refers to the various methods used for the reduction of *dislocated malar bones* and *zygomatic processes*, such as the *towel clip method of Gill*, the *intra-antral method of Shea*, and the *method of Gillies*. In many cases the aid of an orthodontist or a surgeon specializing in diseases of the mouth is necessary.

**IONIZATION.**—While nasal ionization has come to the fore during the past few years as a suitable treatment for hay fever and allergic rhinitis, its status is still unsettled. Ionization has been employed for more than a decade by certain rhinologists. A. R. Hollender and M. H. Cottle used it chiefly as a therapeutic aid in simple chronic rhinitis. Its use in nasal allergy is more recent, but sufficient experience has been had with the method to draw some conclusions. Earlier workers have adhered to the employment of a weak (2 per cent.) zinc sulphate solution as the electrolyte. Warwick, Alden and others prefer an electrolyte of 3 metallic chemicals, zinc, cadmium and tin. It is doubtful whether the latter has any advantage over other solutions for the electrolytic purpose.

L. B. Bernheimer (J. A. M. A. 106: 1980 (June 6) 1936) reports on the clinical results obtained through zinc ionization on the nasal mucous membrane of 25 individuals suffering from *hyperesthetic rhinitis*, and 10 with *seasonal hay fever*. Two patients suffering from hyperesthetic rhinitis developed *anosmia*. Both of these patients had a normal sense of smell before ionization but lost the ability to detect unpleasant, pungent or mild, or pleasant odors within 24 hours after ionization. Both complained of associated *taste disturbances*. This unfortunate complication

persisted for 4 months with 1 patient and for 7 months with the other. As neither was benefited by the ionization treatment, these complications resulted in most unpleasant situations. It should not be forgotten that many persons suffering from hyperesthetic rhinitis have disturbances of the sense of smell resulting from the disease process itself. The rhinologist, therefore, for his own protection, should test the patient's sense of smell before employing ionization. One patient developed a *unilateral headache* referred from the eye on the affected side to the lower occipital region and down into the neck and shoulders. The pain was typical of the syndrome described by Sleuder, sphenopalatine neuritis. It persisted for 3½ months with short periods of remission following application of cocaine to the sphenopalatine foramen. The patient refused to submit to alcohol injection. The author concludes that the clinical course of hyperesthetic rhinitis was influenced in only 5 per cent. of the 25 patients who were treated with ionization. The clinical course of hay fever was not altered by the use of ionization, and ionization of the nasal mucous membrane carries a definite risk of complications.

It should be added further that the possibilities of *local tissue injury*, at least for a brief period, must be entertained. L. W. Dean (Ann. Otol., Rhin. and Laryng. 43: 326 (June) 1936) believes this period is about 2 years.

In discussing late *changes in the mucosa of the frontal sinuses and nose* of dogs following ionization, B. J. McMahon's (Arch. Otolaryng. 22: 454 (Oct.) 1935) report shows fibrosis of the subepithelial tissues with marked hyperplastic changes in the bone at the end of 12 weeks. There was an eventual transition of the epithelium to a cuboidal type over the areas of greatest destruc-

tion. The various steps in the process are shown by photomicrographs of the mucosa of the experimental animals, taken at periods of from 2 to 12 weeks after ionization. The author feels that these same changes taking place in the human nose after ionization, depending on the individual reactions, might lead to permanent atrophy of the glands and symptoms arising from compression of the nerves. It would naturally take some time for such changes to attain their maximum, and he believes that the result would be a premature "nasopause."

In summarizing it can be said that:

1. Zinc ionization is a nonspecific local procedure suitable for nonseasonal types of allergic rhinitis, especially after immunization and other methods have failed to bring about a relief of symptoms.

2. It should not be heralded as a cure, in spite of permanent relief of symptoms in some cases.

3. The procedure merits application only after a careful, comprehensive study of each individual case to establish a rational indication.

**COMMON COLD.**—The common cold remains the problem of considerable investigative effort because of the untold suffering it produces through its complications and because the economic loss in time and wages is greater in this condition than in any other disease that affects the population at large. During periods of influenza epidemics, the common cold is often mistaken for the former condition, resulting in lack of proper treatment and leading to serious consequences. Again, there is much confusion between the common cold and hay fever.

**Etiology and Pathogenesis.**—In discussing the prevention of common colds, P. H. Long (J. Michigan M. Soc. 34:157 (Mar.) 1935) evaluates

the various prophylactics that have been used for the prevention of this common malady. He has endeavored to determine the true part played by bacteria in the course of colds. He demonstrated that 2 main types of cellular response are found in the nasal secretions from patients with colds. One is characterized by an early predominance of phagocytic and epithelial cells in the secretions, while in the other type, polymorphonuclear, neutrophilic leukocytes predominate from the beginning of the infection. Seven first day specimens of nasal secretions showed a predominance of polymorphonuclear, neutrophilic leukocytes, and 4 were practically free from bacteria when cultures were taken on blood agar plates, while 3 contained thousands of microorganisms. Of 8 first day samples of nasal secretions in which monocytes and epithelial cells predominated, 5 showed an abundance of organisms and 3 were practically sterile. It is evident that on the first day of colds it is not possible to correlate the presence or absence of bacteria with a polymorphonuclear, neutrophilic leukocyte response. As streptococci, staphylococci and pneumococci were the organisms generally found in these secretions, this lack of correlation assumes added importance. After the fourth day, the polymorphonuclear, neutrophilic leukocytes averaged 90 per cent. of the total cells present in the nasal secretions. Nevertheless, a scanty bacterial growth was obtained from 18 of 65 specimens examined in the late stages of these colds. The purulent character of the nasal secretions in the advanced stages of colds is not dependent on the presence of numbers of bacteria. The lack of correlation between the bacterial content and cellular response of the nasal secretions is considered to be evidence of a lack of pathogeny on the part of these bacteria in the course of colds.

Therefore, it may be assumed that these organisms are present in the nasal secretions because these secretions constitute a medium favorable for bacterial growth. If true, the failure of bacterial vaccines to modify the severity or duration of uncomplicated colds can easily be understood.

C. H. Browning (Glasgow M. J. 123:329 (June) 1935), in his summary of the causation of the common cold states that:

1. The common cold is, at least in some instances, due to an agent which is not habitually harbored by those attacked. This is proved by the outbreak of epidemics in isolated communities on the occasion of the first visit of strangers after an interval of no communication.

2. Evidence that an infective agent of the filter passing type is responsible is furnished by the transmission of colds to quarantined human subjects and chimpanzees by the intranasal instillation of sterile filtrates of the nasal secretions of persons in the early stage of colds. The causal agent can survive for a considerable period outside the body, and is capable of proliferation in culture medium *in vitro*.

3. It is not determined whether the ordinary pathogenic bacteria which may occur in the upper respiratory tract are ever by themselves the causal agent of coryza, although there is no doubt that as superadded infections they are important in aggravating the condition and especially in bringing about complications.

4. The incidence of colds is to a great extent independent of climate but has some relation to weather. Thus, a sudden fall in temperature tends to be followed by an outbreak, owing, in all probability, to a lowering of resistance of the tissues. Nothing is known re-

garding factors that may influence the virulence of the causal agents.

5. There is little or no evidence that the incidence of colds in a community is related to the general habits of living of its individual members.

**Treatment.**—On the mistaken hypothesis that the common and visible bacteria discovered in the respiratory passages were of etiologic significance, the medical profession and the public have used many types of respiratory or "cold" vaccines for the prevention of the common cold. There is no proof that such vaccines exert any specific protective action, and if there is any value in the procedure, it is likely that immunity is enhanced against the action of these organisms only as secondary invaders or for some other reason still undetermined. Perhaps the only virtue in the periodic use of such vaccines lies in a nonspecific action of foreign protein on the autonomic nervous system.

In the treatment of the acute attack, several measures are of value. These may be grouped under 2 general heads: (1) those measures which constrict the mucous membranes of the nose and permit the passage of air over them; (2) those which open the peripheral vessels. In the first category will be found the **shrinking solutions and applications**; in the second, a **warm room and warm bed, a hot bath, the mustard foot-bath, hot drinks, acetylsalicylic acid, quinine, powder of ipecac and opium, papaverine**, and many other drugs. The chief concern in treatment is with the complications that result from the obstruction of the sinuses and the irritation of the lower respiratory passages.

In J. S. Stovin's (M. Rec. 142:505 (Dec. 4) 1935) experience, the most effective method for treating colds and acute sinusitis in children is the instillation of **mild vasoconstrictors**, followed by **gentle suction**. Strong vasocon-



strictors and germicidal agents are to be avoided. The use of tampons is contraindicated. To prevent colds, proper air-conditioning of homes is important. Rooms are generally overheated, and there is usually too little humidity. **Ultraviolet irradiation** has been recommended. A **change of climate** is of benefit, the southern parts of Florida and California are particularly recommended. The common cold is just as prevalent in children who have had their tonsils and adenoids removed as in other children.

In the Semon Lecture 1935, St. C. Thomson (J. Laryng. and Otol. 51:1 (Jan.) 1936) limits his review of the defenses of the airways to the local means of protection in normal conditions of health. These are reinforced by such prophylactic weapons—particularly in disease—as antitoxins and other antibodies, opsonins and phagocytosis, bacteriolysins, leukins and other germicidal substances, and the army of reserve defenses that maintain the normal state of immunity. These local defenses are so effective in health that it is difficult to produce pulmonary infections by inhalation or insufflation of organisms under normal conditions. He discusses the complexity and perfection of these defenses and hopes to encourage interest in normal processes as a necessary first step to the study of disease. Biology is opening up possibilities of discoveries that will enlarge the conquests of Pasteur, Koch and Lister. This may lead to knowledge that will avert or cure many common human ailments. These studies should help to explain why removal of a focus of infection, or why operations, however radical and brilliant, often fail to cure.

**ALLERGY.**—J. A. M. Cameron (J. Laryng. and Otol. 50:493 (July) 1935), in an investigation of the part

played by allergy, or sensitization, as a factor in predisposing the mucous membrane of the nasal passages and the paranasal sinuses to infection, and its bearing on the treatment of disease of these cavities, states that in allergic diseases that affect the nasal cavity there is always a primary pathognomonic excess of eosinophils in the nasal discharge and in the exudate from punctures. The nasal mucosa and the paranasal sinus mucosæ present an unmistakable eosinophil infiltration, as do the polypi arising from these structures. The eosinophils are of 2 types: the bilobed, with coarse granules; and the mononuclear, with much finer granules. The latter are more abundant in chronic lesions; the former in more acute lesions. It is believed that these cells neutralize some substance liberated in allergy, or that they are a chemotactic response to its stimulus. The author found no evidence that these changes are due to microorganisms. The evidence as to whether allergy prepares the nasal mucous membrane for infection by microorganisms is difficult to assess; allergy has no marked effect as far as statistics show. When infection supervenes, the mucous membrane shows diminution or disappearance of the eosinophils. Confirmatory x-ray evidence is submitted.

In *treatment*, due regard must be paid to the allergic and local nasal aspects. A common practice when food allergies are suspected is to use **elimination diets** for the diagnosis and treatment. In this way, offending substances are discovered, and **desensitization** is attempted by administering slowly increasing doses. It has been shown that the injection of a small dose of antigen into an animal prevents its being shocked by injection of the same antigen introduced in a larger dose some hours later. In cases of *food allergy*, the two methods based on this principle are that

of the small meal and peptone therapy. Cameron concludes that allergic manifestations may have a common genesis in some form of metabolic poisoning which is usually amenable to detoxication.

In discussing allergy and its *relationship to sinusitis and allied nasal conditions*, A. I. Cohen (Arch. Otolaryng. 21:265 (Mar.) 1935) believes that early failures in testing are due to using too few allergens and not paying enough attention to foods. He finds that the pressure puncture method is the most satisfactory, the reactions being more uniform and more easily tabulated. He uses dry allergens and Ringer's solution, which is less irritating than sodium hydroxide. The production of a wheal is not necessary, since hyperemia greater than that seen in the control area is considered positive. **Dietary control** yielded the author the best results. This method of treatment was used in 23 cases of sinusitis alone or in combination with hay fever, asthma, or disturbances of the gastrointestinal tract, with the following results: entire relief, 49 per cent.; much relief, 34 per cent.; some relief, 6 per cent.; and failure, 11 per cent.

A study of allergy in *relationship to sinus disease* was made by the late W. V. Mullin (S. Clin. North America 15:839 (Aug.) 1935) on a series of 216 patients who came to the clinic for operation. He found that allergy was present in from 30 to 35 per cent. of all cases of chronic infection, and states that an eosinophil count of more than 3 per cent. was considered at least significant. More important emphasis, however, was laid on an increase of eosinophils in the blood. He found no improvement from the use of calcium or acids by mouth. The best results were obtained by regulating the **diet**; often all known irritants were removed.

Surgical procedures were restricted to **resection of the septum, removal of obstructing polypi, and simple drainage of a suppurating sinus.**

In discussing *nasal manifestations of allergy in infancy and childhood*, K. D. Figley (Ohio State M. J. 32:312 (Apr.) 1936) states that many children are sensitive to a combination of various groups of pollens, so that their symptoms persist from early spring until late fall, with short remissions corresponding to the brief intervals between pollen seasons. In children, pollen hypersensitivity takes the form of an almost constant or frequently recurring "cold" with watery or mucoid nasal discharge and intermittent nasal blockage. The author states that he has of late seen a number of children in whom pollen sensitivity was pronounced by their second year.

The *symptoms of perennial allergic rhinitis* are similar in every respect to those of the seasonal type, except that they occur at any time throughout the year. Here again, one is confronted with the infant or older child, the subject of constant so-called "colds" or "bronchitis." These are the sniffy, wet-nosed youngsters, many of whom are undersized and undernourished, with typical adenoid appearance, in spite of one or more operations for the removal of tonsils and adenoids. In infancy, the causative allergen is almost certain to be due to food sensitivity, usually 1 or 2 of the cereal-milk-egg combination. As the child grows older, the natural tendency is for spontaneous desensitization to foods, while inhalant sensitivity gains a foothold. Occasionally, food sensitivity persists until puberty, and combined with inhalant sensitivity, complicates the problem.

The majority of children from the ages of 4 on up with perennial allergic rhinitis are pollen sensitive. In addition,

they are sensitized to one or more additional inhalant allergens, the most common being house-dust. In the seasonal pollen cases of allergic rhinitis, asthma occurs as a complication, or rather as part of the respiratory mucosal hypersensitiveness, in from 40 to 60 per cent. of cases.

There are varying degrees of nervous irritability due to allergic intoxication, ranging from the whiny do-nothing child to one that is highly excitable. Regarding the complication of allergic rhinitis by superimposed infection, it is inevitable that sooner or later, bacterial infection will gain a foothold on the swollen, edematous, allergic mucosa.

The diagnosis of allergic rhinitis concerns its differentiation from infectious rhinitis. The *treatment* consists of **elimination, avoidance, and desensitization**. A plea is made by Figley for early recognition and diligent treatment of the allergic infant or older child.

V. Hlavacek (Monatschr. f. Ohrenh. 69:1153 (Oct.) 1935) shows that *eosinophilia* of the tissues is a constant sign of allergic disease. He detected a mild degree of eosinophilia in hay fever, a more severe form in vasomotor rhinitis, and the most severe eosinophilia in the polypi of patients with asthma. He states that if eosinophilia is observed in the polypi, other signs of allergic disease should be searched for. He reports further how he effected an increase in the number of eosinophils in the nasal mucosa of guinea pigs. As a sensitizing substance, scales from horses were used. It was found that in the sensitized animals, in which shock was elicited by the parenteral injection of the antigen, the number of eosinophilic leukocytes was slightly increased in the nasal mucosa. However, when shock was produced in sensitized animals by the direct action of the antigen on the mucous membrane of the upper respira-

tory passages, considerable eosinophilia of the nasal mucosa was the result. The increase in the number of eosinophils in the tissues follows the same laws as the increase in the blood: it reaches a peak several hours after anaphylactic shock.

F. M. Rackemann (J. A. M. A. 106: 976 (Mar. 21) 1936) discusses *history-taking* in allergic diseases. He states that the successful treatment of hay fever, asthma and eczema, like the successful treatment of other diseases, depends on a complete understanding of the patient and his particular problem. In the allergic diseases, this is especially true because, as Pirquet has described, the symptoms depend on the peculiar capacity of the individual to react toward certain foreign substances. First of all, the physician must know whether or not the symptoms of which his patient complains are of allergic origin. The 5 symptoms and signs which are characteristic of each manifestation of clinical allergy and which, when found, are helpful to the diagnosis are: 1. A characteristic symptom dependent on a characteristic local pathologic condition. 2. The presence of some other allergic symptoms in addition to the first. 3. A positive family history of allergy. 4. Positive skin tests. 5. A blood eosinophilia. Any of the allergic diseases may coexist with and be complicated by some other disease. The allergic diseases are common but "cures" are not so common. Since the fundamental nature of allergy, of the capacity to develop sensitiveness and then to react to the specific substance is still unknown, present interest, at least from the practical point of view, concerns the exciting cause of the symptoms. Diagnosis of the exciting cause of asthma, sometimes referred to as the "trigger" mechanism, rests on 3 factors, which in the order of their importance are the history, the physical examination and the skin tests. It is the history,

however, which, from the practical point of view, becomes the chief diagnostic measure. The author summarizes his article:

1. The clinical history is of primary importance in the diagnosis and treatment of the "allergic" diseases.

2. Dates in the history are not only the accurate expression of time, but are essential to the accurate expression study of hay fever, of asthma, and of eczema.

3. To account for all the time is to learn, in many cases, not only why the attack began but why it ended, and then later why the free period in turn ended.

4. When the history is not long, or contains only a few events, further history can be "made."

5. In atopic dermatitis (eczema) the history may be quite as important as it is in eczema.

The influence of the *spleen* in allergic conditions is described by C. R. Griebel (Arch. f. Ohren-, Nasen- u. Kehlkopfh. 140:101, 1935). He made sugar tolerance tests on rabbits, some of which had first been sensitized by repeated subcutaneous injections of small amounts of an allergen. The allergic animals showed considerable eosinophilia. In tolerance tests it was proved that the metabolism of sugar is disturbed in these animals, in that the blood sugar reaches an unusually high level and remains at this high level for much longer periods than it does in animals that have not been made allergic. However, when the allergic animals were given an injection of an extract of spleen (free from protein, sugar and lipoid) previous to the sugar tolerance test, the reaction was considerably reduced toward the normal. In other experiments the reticuloendothelial system of the animals was blocked. Griebel concludes that clinical observations as well as experiments on animals indicate that the spleen exerts a considerable influence on the eosinophilic

blood picture. It was found that the administration of an **extract of spleen** in allergic disturbances (bronchial asthma, vasomotor rhinitis and hay fever) produces the best results in *vasomotor rhinitis*; in hay fever, the effects are less favorable, and in bronchial asthma, they are least favorable. To be sure, the eosinophilia was reduced in all of these conditions, but only in vasomotor rhinitis was this reduction accompanied by a cure. Griebel considers spleen therapy promising in the treatment of allergic disorders.

**EYE COMPLICATIONS.** — In discussing *inflammatory exophthalmos* in catarrhal disorders of the accessory nasal sinuses, M. Cohen (Arch. Ophth. 15: 457 (Mar.) 1936) states that the venous circulation plays the important part. The veins, being valveless, permit infection to be carried to and from the orbit. The lesions in the orbit depend on the severity of the sinus infection. During the past 3 years, 1817 patients with sinusitis have been treated in the wards of the Manhattan Eye, Ear and Throat Hospital. In 22 cases the condition was complicated by inflammatory exophthalmos. There were 2 deaths; 1 from meningitis and 1 from septic thrombosis of the cavernous sinus. Among the 22 patients with inflammatory exophthalmos, there were 11 with acute ethmoiditis who were treated with medication to the eye and the nasal cavity. The remaining 11 patients were treated by conservative surgery; 5 by incision and drainage for subperiosteal or orbital abscess, 4 by external ethmoidectomy with opening of the sphenoid, and 2 by surgical treatment of the frontal and ethmoid sinuses. The ocular signs of inflammatory exophthalmos are self-evident, except in the mild acute cases in which the condition is caused by an inflammatory edema of the retrobulbar tissue. In this condition

the exophthalmos, the ocular inflammation, and the nasal condition are mild and respond rapidly to appropriate treatment. The patient recovers in a few days.

The ocular and nasal signs in the more acute and subacute types are more marked and distinctive and are discussed with an illustrative report of a case. Cases of *empyema* of any of the sinuses, with *rupture into the orbit*, are recognized by a local swelling with fluctuation over the area involved, accompanied by general symptoms, such as pain, headache and increased temperature. Rhinologic and x-ray examination give positive evidence, in addition to swollen nasal mucosa and discharge. The acute symptoms in this type persist for about 3 or 4 weeks, after which the ocular signs gradually disappear. In the chronic type, the symptoms are similar to those observed in the subacute type, but they are prolonged over a period of 8 months or longer.

The exophthalmometer is an aid in diagnosing doubtful cases of exophthalmos; this instrument also assists in judging the results of treatment. The treatment in these cases is concerned not only with the ocular condition, but also with the sinus disease which is its primary cause. The prognosis is generally favorable in all types of cases, especially if the ocular and general symptoms are not progressive.

A case of *unilateral blindness* with a latent closed *empyema of a posterior ethmoid cell*, with recovery following operation, was reported by L. Cerise, J. Ramadier and H. Guillon in 1934. A man, aged 32, entered the hospital with the complaint of loss of vision in the left eye and periorbital pains for the previous 8 days. Examination revealed a slightly swollen and edematous papilla and an enormous central scotoma in the left eye. Vision was limited to a narrow

crescentic area with its concavity downward. There was no sign of nasal supuration, and the x-ray examination showed no evidence of involvement of the sinuses. Since the vision rapidly diminished to complete blindness, **resection of the septum** and exploration of the posterior sinuses were done. Two c.c. of thick fetid **pus** was **evacuated** from a **posterior ethmoid cell**. The operation was not extended farther. Improvement was immediate, and at the end of the eighth day the visual field and the papilla were normal, and vision was  $\frac{9}{10}$ . From an ophthalmologic point of view, this case was one of optic neuritis with functional signs, quite different from those of the classic form. The authors agree with Portmann and Pesme that the association of functional signs of retrobulbar neuritis with papillary lesions and painful symptoms suggests that these ocular disturbances originate from an infected sinus. In such cases, even when the nasal examination gives negative results, an early **exploratory operation** on the ethmoid and sphenoid sinuses is indicated.

Bonnet, Sargnon and Paufigue reported a case of a boy, 13 years old, who complained that with his right eye he had been seeing many *black spots* in his field of vision for 18 days. Visual acuity was normal. The anterior segment and vitreous were normal. The papilla presented a hazy outline, the veins were dilated, and a circle of edema could be observed adjoining the disc on the nasal side. The temporal segment was normal. The visual fields had the usual extent, but there was some constriction for colors more especially for green. The x-ray photograph of the head, the urine and the Wassermann test were normal. The right nasal passage showed signs of obstruction. The edema of the fundus increased. Several **polypi** were re-

moved from the nose, and recovery was immediate.

Among the medical problems solution of which depends on the collaboration of neurologists, ophthalmologists and rhinologists, is the problem of *acute retrobulbar neuritis*. A large number of patients who recover spontaneously are later found to have multiple sclerosis. An increasing number of patients with bilateral subacute retrobulbar neuritis (atypical cases) have later manifested multiple sclerosis in spite of early operation on the posterior sinuses.

G. Weill and J. Nordmann discuss retrobulbar neuritis, sinusitis and *multiple sclerosis*. They report 2 cases, in both of which multiple sclerosis became manifest 3 and 6 years, respectively, after apparent recovery. Both patients had suppurating sinuses which were operated on. Atypical retrobulbar neuritis is attributable, in general, to disease of the chiasmal region or of the posterior sinuses. Behr produced signs of multiple sclerosis in rabbits by transplanting mucosa from the sinuses into the cranial cavity. At least in some cases of multiple sclerosis and retrobulbar neuritis, the bucconasal route of infection must be assumed. "Interventionists" should review their old case histories to determine the number of cases in which multiple sclerosis has developed, and to compare their findings with the statistics in cases in which operation was not performed. If the incidence of multiple sclerosis in such cases is really rarer after curettage of the sinuses, Weill and Nordmann will join the ranks of interventionists in order to try to prevent the onset of multiple sclerosis. Spontaneous recovery nearly always takes place in cases of retrobulbar neuritis.

In a study of 120 patients with *chronic posterior uveitis*, W. D. Gill (Ann. Otol., Rhin. and Laryng. 44:486 (June) 1935) found sinus infections in 48 per

cent., the majority of which were of the ethmoid sinus. The duration of the antecedent sinusitis averaged slightly over 2 years. Gill claims that low grade infection affects the vascular tunic of the eye, especially the choroid vessels. There is a liberation of enzymes through disintegration of choroid cells. These act on the uveal pigment, converting it into a substance which is subsequently absorbed and acts as an allergen. Such patients, when tested with uveal pigment, nearly all gave heightened reactions. It is often difficult to eradicate the pathologic process in the sinus on account of a low grade osteitis with tendency to recurrences. Patients with such a condition require careful postoperative treatment.

A case of *ophthalmoplegia* associated with bony changes in the region of the sphenoidal fissure is described by C. B. V. Tait. The patient was a girl aged 17 years, who had been in normal health until sharp pain developed in the right eye, extending to the right temple. With this, vomiting began. There was complete paralysis of all the extra-ocular muscles. The pupil was semidilated and sluggish. Ptosis was complete. There was some hyperesthesia of the right supra-orbital nerve, while corneal sensation was impaired. The fundi were normal. Ten days later the left eye became similarly affected. X-rays showed extensive *erosion in the region of the sphenoid sinus*; with destruction of the clinoid processes of the sella turcica, together with most of its floor; but there was no definite evidence of tumor. The interpretation favored erosion in this region rather than absorption by pressure.

There was a rapid response to **x-ray therapy**. Four years and six months after the onset, the patient was in good health and had recovered completely except for some residual weakness of the external rectus muscle of the right eye.

Clinically, the case shows many of the features which characterized the condition described by James Collier in 1921, and termed "*rheumatic periostitis of the sphenoidal fissure*."

**OZENA.—Treatment.**—In discussing the surgical management of ozena, S. M. Morwitz (Illinois M. J. 69:130 (Feb.) 1936) describes the 2 recognized clinical types of atrophic rhinitis. The primary atrophic rhinitis or rhinitis atrophicans fetida et crustosa which is on a metabolic or endocrine basis, and the secondary atrophic rhinitis which is associated with chronic paranasal sinusitis. The primary type eventually leads to true ozena with its characteristic fetor, while the secondary form occasionally develops crusts and fetor of a mild nature. At the Research and Educational Hospital of the University of Illinois, the technic as described by A. Wachsberger was used 7 times bilaterally in 2 cases and unilaterally in 3 cases. The advantages of the **Wachsberger operation** are as follows: The operation is done through the nose. It is done without any incision into the nasal mucosa, thus preventing permanent openings into the antrum. His method is applicable and as successful in persons with antrums of normal size. Mobilization and transposition of the most anterior part of the lateral wall result in narrowing of the nasal cavity to a greater degree and make this method suitable for advanced cases. It is easier to perform technically, and the after-treatment is simple. The author states that the postoperative reaction of the atrophic nasal tissue is startling. The inferior turbinate, especially, becomes enlarged, hyperplastic, and its mucosa assumes a pinkish hue. The fetor immediately disappears and, if good intranasal narrowing is maintained, crusting becomes a negligible factor. The after-

treatment requires little time and effort. An interesting observation is the freedom of nasal respiration in spite of the greatly reduced nasal chamber space. Two patients claimed they could distinguish certain odors. The patients take on new hope and with it a markedly improved psychologic state. The writer, after having experimented with a number of recognized medical and surgical types of therapy, considers, at present, the **Wachsberger modification** the most rational and practical form of therapy for physiological cures in cases of genuine ozena.

**SINUSES.—Anatomy.**—G. Pancrazi (Boll. d. Soc. med.-chir. di Modena 34:169, 1934) describes a specimen in which the posterior *ethmoid cells* were enormously developed. They invaded the lateral portions of the sphenoid body, the greater wings of the pterygoid processes, and the orbital processes of the bones of the palate.

The ethmoid cells of 5 fetuses observed at 8 months and of 35 observed at term were studied by G. E. Jayle (Ann. d'anat. path. 12:876 (July) 1935), who found 2 transverse laminae (the anterior and posterior ethmoid laminae) which divided the cells into 3 spaces. Within the middle meatus there are 2 secondary laminae, the bulbar and the unciform. These divide the middle meatus into 3 portions: medially, the middle meatus proper, and externally, the unciform cavity in front of the bullar cavity behind. This arrangement agrees in the main with the conclusions of Mouret, who described in the adult, under the name of laminar roots of the turbinates, the bony plates mentioned by the author.

**Physiology.**—H. K. Tebbutt, Jr. (Arch. Otolaryng. 22:733 (Dec.) 1935) studied the effect of physical agents on the temperature of the nasal sinuses.

He conducted experiments on 3 patients whose sinuses were accessible by reason of previous radical surgical procedures, and in whom there was no acute infection present at the time of the experiments. Various agents producing heat and cold were applied over the sinus, and the intrasinus temperature was recorded. It was found that ice compresses, an icebag, a hot-water bottle, an electric heating pad and hot compresses all failed to affect the intrasinus temperature. When the infrared rays or the high frequency oscillating current were used, there resulted a drop of 1° F. in the temperature of the sinus. This drop is explained as being due to evaporation of the increased nasal secretions resulting from the agents. The author believes that these agents have some value because of this increased discharge, which improves drainage and hastens resolution.

**Diagnosis.**—*X-ray.*—An attempt is made by V. Soldatini (Arch. ital. di. otol. 47:349 (May) 1935) to define normal and abnormal sinuses from x-ray pictures. According to his criterion, the normal *frontal sinus* is one with regular outlines and without eccentric or walled-off portions. The external boundary of the normal frontal sinus is composed of two-thirds of the supra-orbital margin, and the superior boundary, of  $\frac{1}{3}$  of the forehead, there is no extension over the orbit. Normal *ethmoid cells* should not extend beyond the boundaries of the ethmoid bone. Cells extending upward into the median orbital wall, directly into the frontal sinus or downward into the maxilla are considered abnormal. A normal *maxillary sinus* should occupy the greater part of the maxilla and should have regular walls and no partitions. In a study of 200 cases, the author found the greatest number of abnormalities in the frontal sinus and the least in the maxillary sinus. Also, it is significant that the abnormal sinus

is more frequently affected by disease than the normal sinus.

J. Van der Hoeven Leonhard (Ann. d'oto.-laryng. p. 526 (May) 1935) seems to think that the anatomic structure and size of the *frontal sinus* have much to do with the tendency to chronicity in some cases. When the anteroposterior diameter is less than 18 mm., chronic trouble is rarely found. Sinuses measuring from 18 to 30 mm. are frequently the seat of chronic infection which can be cured by intranasal enlargement of the nasofrontal duct. When the diameter exceeds 30 mm., the author feels that an external operation is required.

E. H. Shannon (J. A. M. A. 106: 599 (Feb. 22) 1936) investigated the *maxillary antrum* radiologically and correlated the x-ray and operative findings. In 130 cases, chronic maxillary sinusitis with more or less well marked mucosal thickening was the major finding reported. In 127 cases the diagnosis was confirmed. In 18 cases of the 127, polypi of small size were found at operation which had not been seen in the x-rays. Three cases considered acute by x-ray examination were found to be of chronic type. Of 106 cases, polypoid degeneration was reported as the outstanding feature, with subsequent operative confirmation. Four antrums in which polypi were reported were found to contain cysts. Of the 102 remaining, in 2 instances pus was reported to be present in quantity and was not evident to the surgeon; in 4 cases pus in quantity was found and had not been reported; in 2 cases polypi of 1 cm. or more in diameter were removed when only mucosal thickenings had been reported. Thirty-eight cases were described as showing evidence of barely demonstrable osteitic reaction, with no definite mucosal thickening, pus or polypi present. They were considered as representing residual changes from an old infection not active



at the time of examination. Of this group, 6 contained one or more very small polypi, not visible preoperatively or on reëxamination of the film. In 22 cases, frank empyema was reported and confirmed at operation. Of these, 10 were reported by the surgeon to have contained polypi, the presence of which was entirely masked in the x-ray pictures by the contained pus.

A survey of the tabulated results of these cases indicates that the x-ray diagnosis of chronic maxillary sinusitis made on "plain" x-ray films was essentially correct in almost every instance. Shannon believes that the presence of polypi in an antrum containing definite mucosal thickening, especially if an osteitic reaction is present, does not materially alter the clinical conduct of the case. In the 38 cases of the 296 described as representing the end-result of an old healed infection, this may not apply. They form the borderline group, and it will be seen that, while definite evidence of disease was not lacking, a detailed description of the pathologic changes present was not accurate in 6 of 38 antrums examined. In this group only a slight haziness was observed radiologically over the suspected antrum, with no definite pus or polyp formation evident. The periosteum in several instances was apparently thickened, while at operation the mucous membrane was found to be adherent; the bone bled readily and was hard to the curet. He feels that the knowledge of the presence of even slight polypoid degeneration of the mucosa might influence treatment in such cases as indicating the probability of reinfection when healing was considered to have occurred. He believes that if doubt still exists, an opaque medium may well be used to fill the antrum, by whatever method is preferred by the operator. The preliminary plain films will then establish the presence of

minimal osteitic reaction; the iodized oil may reveal the slight associated polypoid degeneration of the mucous membrane.

In a review of the *Proetz lipiodal study of sinuses* (*Eye, Ear, Nose and Throat Monthly* 15:284 (Sept.) 1936), G. M. Coates states that the displacement method of introducing radiopaque substances into the nasal accessory sinuses is not only safer, but far more effective than any injection procedure. Briefly stated, the technic consists of the patient reclining with chin up and head extended until the chin and external auditory meatus are in a vertical line. Then about 0.5 c.c. of the solution (one of the commercial radiopaque oils advantageously diluted with olive oil or liquid petrolatum, 1 to 4 times) is expressed in the floor of the nose, one nostril stopped by the finger and gentle suction applied to the other by a suitable apparatus (suction pump delivering 180 mm. negative pressure, Politzer bag, or special Proetz hand pump) while the patient is instructed to close the nasopharynx by producing the "K" or "coconut cake" sound, thus bringing the soft palate in contact with the postpharyngeal wall. More oil is now placed in the nose and the process is repeated until the sinuses will not take any more oil. From 5 to 10 c.c. may be used, depending upon the size of the cavities to be filled. The introduction usually alternates between the two nostrils and the whole operation should not take more than from 1 to 3 minutes. The patient now sits up with the head a little forward so that surplus oil will drain from the nose and he is then ready to be filmed.

The advantages of pictures taken from sinuses thus treated include the following:

1. The walls of the sinus cavities are better outlined, particularly the ethmoids and sphenoids, so that recesses,

extensions and aberrances of these structures are plainly indicated.

2. Intrasinus pathology is indicated. In the normal sinus the ostium is unobstructed and should freely admit the oil. The sinus mucosa is smooth in outline and thin. In such a sinus the x-ray plate shows the bony wall of the sinus and almost immediately next to it the dark shadow of the radiopaque. There is usually a fine, clear line between these two, but if this line is widened, it means thickened, and therefore diseased, mucous membrane. Irregularities in the outline, except in the case of bony septa and excrescences, have the same meaning. A polyp, cyst or neoplasm stands out prominently in relation to the contrast medium employed. A sinus may be so filled with pathological tissue that only 1 or 2 drops of the oil can be introduced, and an allergic swelling is clearly outlined as a definitely thickened mucosa.

3. Estimation of the patency of the orifice. If the sinus does not contain oil, barring errors of technic, it means either that the ostium is closed or that the sinus is full of pathological material. The pathology causing closure of the ostium includes septal deviations and spurs, hyperplastic or hypertrophic turbinates or polypi. When some sinuses fill and others do not, the evidence that the above conditions are true is presumptive.

4. Estimation of the emptying time and, therefore, of the activity of the cilia of the sinus mucous membrane. The normal emptying time of the sinus varies, of course, with a number of factors, such as position of the head, size of the cavity, and viscosity of the oil, but, in general, all traces of oil should be gone in 72 hours. If emptying is delayed beyond 96 hours, it is evident that ciliary activity is impaired or perhaps lost—there being a badly

damaged mucous membrane lining the sinus.

5. In allergy. A film taken during an allergic attack may show anything from a moderate thickening of the mucosa to a total occlusion of the sinus by swollen and edematous mucosa. Another film taken in 24 hours after recession of the attack may show a normal or only slightly thickened mucosa, unless, of course, other pathology coexists. From the observation it becomes evident that a second 24-hour check film should be taken before an operation procedure is contemplated on a sinus.

**Treatment.**—J. N. Fishbein and E. J. Staff (Rhode Island M. J. 18:129 (Sept.) 1935) report results with **long wave high frequency medical diathermy** in 400 patients (6500 treatments) suffering from acute or chronic hyperplastic rhinitis, hay fever, asthma or some form of sinus infection. The infection was chronic in 355 of the cases. The positive electrode, consisting of long, narrow ( $\frac{3}{8}$  inch) ribbons of closely woven copper strands with a resistance of 60 ma. per square inch, was placed in the nose and the negative electrode on the forehead. The positive electrodes were wrapped in long fiber cotton, soaked in 7 per cent. **solution of mild protein silver** with the addition of a small amount of **ephedrine**, and inserted into the middle meatus as far back as the wall of the sphenoid sinus. The dose employed was 300 to 500 ma. for from 15 to 20 minutes. From 6 to 10 treatments were given in each case. The effect of this treatment is to stimulate activity of the mucous glands. Cultures taken before and after treatment demonstrated a reduction of from 70 to 80 per cent. in the number of organisms as compared to the results in controls treated without diathermy in whom the reduction was from 10 to 30 per cent. The authors believe from

the foregoing evidence, as well as from supporting evidence in experimental animals, that by this treatment sufficient heat is produced in the nose to attenuate or destroy many of the surface organisms.

E. von Köhler (Schweiz. med. Wchnschr. 65:395 (Apr. 27) 1935) recommends the **short wave** (frequency of 20,000,000 to 50,000,000) in the treatment of both acute and chronic disease of the *maxillary* and *frontal sinuses*. He claims that many patients now subjected to surgical measures could be cured by this method. In cases of acute involvement the difference between the usual long wave diathermy and the present short wave is astonishingly marked. The generation of heat is from within outward in contradistinction to the older method. Short wave therapy suppresses the sympathetic impulses and stimulates the vagotonic impulses which lead to more permanent dilatation of the capillaries. The electrodes described by the author are constructed of felt soaked in liquid petrolatum and covered with plaster through which the metal contact is entered. This makes for better application to the individual patient.

C. K. Gale (Laryngoscope 45:520 (July) 1935) has used the **ultrashort wave** in the treatment of 50 patients with *chronic sinusitis* with excellent results. Among the typical cases cited is that of an adult with a discharge of 8 weeks' duration, pain in the cheek and x-ray evidence of infection of the ethmoid and frontal sinuses and pus and polypi. The patient was exposed to 10 ma. of 300 watt current daily for 45 minutes. After 4 treatments, all the symptoms were relieved. A child with bilateral chronic ethmoiditis and pus in both sides of the nose had been treated by the usual methods for 6 months without avail. After 8 exposures to the ultrashort waves, the condition

cleared up, and 7 months later, the patient remained cured.

The value of **x-ray therapy** in *chronic sinusitis* is discussed by E. D. Warren (*Ibid.* 45:864 (Nov.) 1935). He reports on 72 cases treated by deep x-ray therapy. Every type of sinusitis has been treated except atrophic rhinitis. It was the author's purpose to determine the value of this form of treatment in all types of cases. On the basis that x-ray is of value in various types of infections and in reducing lymphoid hyperplasia, its application in chronic sinusitis appears rational. In this condition the picture is typically that of an infected mucous membrane with lymphoid hyperplasia and multiple infected glands. It is this selective action of the x-ray having a greater affinity for glandular tissue that makes it a safe and logical procedure. The action of x-ray on sinus mucosa is mainly one of death of the lymphatic cells followed by proliferation of the histocytes.

Due consideration is shown involved structures during treatment by adequate protective coverings. The brain gets a light irradiation, but one that is not injurious. The response to x-ray therapy of chronic sinusitis depends on the selection of cases. In some it is excellent, while others show practically no improvement. In the author's series, 25 per cent. have shown marked improvement, 40 per cent. moderate improvement, 20 per cent. transitory moderate improvement, while 15 per cent. have shown no improvement.

It is emphasized furthermore, that subjective improvement may be had without radiographic improvement. The greatest effectiveness is in the hyperplastic type and allergic or borderline allergic cases with attendant nasal infection. The chronic purulent types of many years and the type having had

many operations show variable responses, most of which are not entirely favorable.

The treatment of *chronic sinus infection* with **undenatured bacterial antigen** is reported by F. C. Kracaw (*Ibid.* 46:26 (Jan.) 1936). The undenatured antigens are made from pathogens isolated by cultures taken from the nasal tract. The technical procedures developed by Krueger for preparing these antigens are described in various published reports. The antigens are employed for topical immunization and for general immunization by hypodermic injection.

A year or more after completion of treatment in a previously reported series of 45 cases, it was found that 28 of the 30 patients considered cured had maintained that status, while the 13 patients classified as presenting satisfactory clinical improvement, all remained in this category. A second series comprising 62 patients showed 52 markedly improved or cured, 2 failures, and 8 patients in whom improvement was only moderate. On a percentage basis, the present series revealed 84 per cent. Patients markedly improved or cured as compared with 66 per cent. so classified in the first series. The improvement in results may be ascribed to a modification of technic involving a more persistent immunizing program.

In properly selected cases it is the author's opinion that topical and general immunization with undenatured bacterial antigens, prepared according to the technic outlined, is the method of choice for the treatment of chronic sinusitis.

H. A. Schatz (M. Rec. 141:28 (Jan. 2) 1935) for a number of years has had excellent results in the treatment of recurrent infections of the *antrum* by following **irrigation with saline solution** with sufficient **insufflation of air** to dry out the residual fluid and then instilling  $\frac{1}{2}$  dram (2 c.c.) of a 10 per

cent. solution of **silver nucleinate**. After the third treatment, he begins using a weak solution of **silver nitrate**, (3 drops (0.186 c.c.) of a 10 to 12 per cent. solution in 1 ounce (30 c.c.) of distilled water). "This is forced into the sinus about one-third at a time. The patient is instructed to throw the head backward, to one side and then to the other and finally forward. These postures are intended to bring the solution into contact with each of the walls of the sinus. The procedure is repeated after each portion of the ounce is injected. No attempt is made to blow out the final amount of solution that remains." The strength of the solution is increased every 48 hours by 1 drop (0.062 c.c.) until a concentration of 7 drops (0.43 c.c.) to the ounce is reached. This seems to be the usual limit of tolerance. If the silver nitrate is not tolerated, the author advises the use of a 5 per cent. **solution of aluminum acetate**.

E. R. Faulkner (Tr. Am. Laryng. Rhin. and Otol. Soc. 41:88, 1935) favors conservative treatment in cases in which the infection fails to clear up after the acute stage. He believes in trying such local measures as **displacement irrigation**, **vaccines**, **diathermy** and **infrared rays**. Should such treatment fail in cases of *chronic infection*, he advises thorough appraisal of the pathologic process before trying surgical measures. Should metastatic phenomena be present and the antrum show a pathologic process, one should not hesitate to perform a **radical operation**. In case of doubt as to the extent of the pathologic process present, he advises **exploratory trephining** of the canine fossa and direct inspection with the nasopharyngoscope. Also, in connection with the disease of the frontal and ethmoid sinuses, the operator must be guided not only by the degree of the local pathologic process but by the

tent of the metastatic phenomena as well.

Occasionally, severe *complications* develop in the course of antrum irrigation.

An unusual complication arising from puncture of the antrum is described by W. F. Swett (Am. J. Ophth. 18:359 (Apr.) 1935). The procedure was immediately followed by *pain in the eye, swelling of the lower lid, flashes of light* and *blindness*. Examination of the fundus showed the vessels of the retina to be completely empty. The picture was like that produced by an air embolus of the central vessels. The fundus was watched closely, and soon the arteries took on rapid clonic dilatation and contraction as a column of blood was seen to advance and recede. "This (pulsation) was transmitted to the veins so that the whole disc had the appearance of pulsating." After 20 minutes the pulsation became less as the vessels filled. The vision was still blurred. Thirty minutes later the patient complained of intense pain in the eye and headache. Examination revealed marked secondary glaucoma (tension, 3 plus) and a hyperemic fundus, both veins and arteries being engorged, owing to secondary relaxation of the vessels. The use of **massage** and **hot compresses** was continued all day. The next day the tension and fields were normal; vision was  $\frac{20}{20}$ , although blurred, and within 3 days everything was normal.

Subsequent to puncture and irrigation of an *antrum*, E. Bruch's (Ztschr. f. Laryng., Rhin., Otol. 26:65, 1935) patient complained of feeling ill but recovered after lying down for a few minutes. The other antrum was then punctured, and immediately after the injection of air, the patient collapsed, went into *clonic spasms*, followed by *coma* and *strabismus*, and *died* within 18 hours. The pathologist could find no demonstrable cause for death at

autopsy. He stated that the 18 hours which had elapsed from the time of the accident was sufficient for any air in the cerebral vessels to have been absorbed. Prof. Gross attributed the death to the use of too strong a solution of cocaine. The author's opinion was that the puncture was made too far forward, in the region where the bone is thick and where the venous plexus about the lacrimal duct is particularly rich, and that there was a regurgitation of air from the punctured sinus into the open veins on the medial wall.

**SINUSITIS IN RELATION TO ARTHRITIS.**—J. J. Littell (J. Indiana M. A. 29:270 (June) 1936) discusses the relation of sinusitis to arthritis. He believes that (1) sinusitis often serves as a most important and frequently unrecognized focus in the cause of rheumatoid arthritis; (2) the systemic disease may often be markedly alleviated or entirely arrested by its proper care; and (3) the area involved in these cases is usually the ethmoid. Sinusitis of some degree is common in temperate climates. His chief interest in it as a source of systemic disease is less in the amount of sinusitis than in the degree of absorption. Since he has approached it in this way, he has had much less disappointment in the care of the condition. Absorption takes place largely from the ethmoid-sphenoid region. A few cases have shown systemic improvement following treatment of chronic maxillary sinusitis. The greatest benefits, however, have accrued from attention to the upper sinuses. Of the 20 cases of arthritis cared for in the last few years, the author has had only 2 serious disappointments. In 1 of these, antral hyperplasia alone was removed. The patient showed no improvement and progressed unfavorably. The second, a severe case with fever, has now cleared up, but only after a stormy 3 years in Arizona. Three

have shown only slight improvement. The remainder have improved from approximately 75 to 100 per cent.

**SINUS DISEASE AND BRONCHIECTASIS.**—The relationship of bronchiectasis to sinus disease has long been an established fact. M. Kartagener and K. Ulrich (*Beitr. z. Klin. d. Tuberk* 86:349, 1935) consider the connection between sinusitis and bronchiectasis as occurring in various ways.

1. Occurrences of bronchiectasis after sinusitis.
  - (a) Aspiration of infected secretion.
  - (b) Aspiration of infected tissue.
  - (c) Transmission of infection by way of lymph channels.
2. Occurrence of sinusitis after bronchiectasis by extension upward of chronic bronchitis, the infected material being frequently coughed up into the nasopharynx.
3. Simultaneous infection of both the bronchi and the sinuses due to exogenous influences (measles, influenza) and parallel development of the mucosal infections. (The *authors* believe that bronchiectasis occurs in patients who are predisposed through congenitally weak bronchial walls.)
4. Congenitally weak and undeveloped sinuses in association with congenitally weak bronchi, which accounts for the parallel development of infections in both places due to the same infective agent.

Eighty-six persons with bronchiectasis averaging 33 years in duration were studied following x-ray examination, and 32 were found to have chronic maxillary sinusitis. In most of the cases the condition was of the hyperplastic type. In many of the patients the frontal sinuses were absent or underdeveloped. For comparison, 100 patients with a history of previous injury to the head were examined, and only 16 per cent. were found to have arrested development of the frontal sinuses as compared to 38.4 per cent. in their series of bronchiectatic patients. The authors believe that the high percentage of small frontal sinuses

was due not to disease of the adjacent maxillary sinuses but to a constitutional endogenous influence, the same that was responsible for the bronchiectasis. They, therefore, conclude that the frequent occurrence of disease in the two locations is the result of a congenital weakness of the organs themselves.

G. E. Hodge (*Arch. Otolaryng.* 22: 537 (Nov.) 1935) observed 37 patients with bronchiectasis at the Montreal General Hospital. He found approximately 75 per cent. had associated sinusitis. The maxillary sinus was most frequently affected. Statistics from various centers show the 2 conditions occurring simultaneously in from 55 to 100 per cent. of the cases.

The recent evidence definitely suggests that some change occurs in childhood which predisposes these patients to subsequent infection of the lungs. Bronchiectasis has been well described as a disease of childhood. It is interesting to note in reports of cases the frequency with which patients with bronchiectasis date their symptoms to early childhood. It has been suggested that atelectasis is the precursor of bronchiectasis in adults. While it is true that there are many exceptions, all the present evidence tends to show that suitable soil is developed in early childhood for subsequent infections of the respiratory tract. Sinusitis which takes part in the involvement of the whole respiratory tract may date from infancy, the constant overflow of secretion being sufficient to keep the bronchial condition active. While some patients with bronchiectasis do not show any evidence of sinusitis, even after the most thorough examination, the possibility that infection of the sinuses might have been present at some time cannot be excluded. In view of the more recent knowledge, it is perhaps reasonable to assume that in patients with bronchiectasis, the sinuses share the primary in-

fection of the whole respiratory tract. Owing to good drainage, the upper portion of the tract clears up, while the extreme degree of pneumonitis present prevents the lower portion from clearing. Considerably more investigation is needed to decide just what part allergy or hypoglycemia plays in sensitization of the whole tract to infection.

In commenting on the *treatment*, the author states that there is general agreement that, once bronchial dilatation has occurred, only **radical surgical intervention**, which unfortunately still has a high mortality rate, is successful in curing this condition. And while operation on the nasal accessory sinuses will not cure bronchiectasis, any **focus** should be, when possible, **removed** before surgical treatment of the lung is instituted.

It is in children that the best results are obtained from conservative treatment, and this should be commenced early. The upper respiratory tract should receive active treatment. This usually means **relief from mechanical obstruction**, resulting in free drainage. **Bronchoscopic suction, postural treatment and vaccine therapy** all have their part. A child with sinusitis, who has frequent attacks of bronchitis and pneumonia, should be regarded as having potential bronchiectasis. He should be carefully guarded so far as climate, diet, contamination from the air, and work are concerned, in order to protect the respiratory tract from further infection.

#### SINUSITIS IN CHILDREN.—

W. Spielberg (Laryngoscope 45:114 (Feb.) 1935) objects to the preliminary removal of the tonsils and adenoids in the presence of a chronic infection of a sinus. He believes that the procedure aggravates the infection and protracts the course of the disease. His advice is not to operate until the disease is cured or at least is greatly improved. He

thinks highly of the use of **autogenous vaccines** made from the collected secretions from the nose, sinus discharge, tonsil exudate, and smears from the pharynx. The initial dose should be small and should be given intramuscularly once a week. Of 44 patients treated with vaccines and other palliative measures, 22 were cured and 18 improved. Where **antrotomy** is indicated, it is done with the patient under general anesthesia. The use of a preliminary **epinephrine pack** decreases the amount of bleeding. The opening is made with the author's trocar, and the sinus is inspected through an antroscope. The opening is enlarged either with a rasp or with a Jensen punch. Packings of iodoform gauze are left in the inferior meatus for 2 days. **Suction, tampons of mild protein silver, and radiant heat, infrared rays or ionization** are used in the postoperative treatment.

In a study in the disorders of the accessory sinuses in *nurslings*, H. Schönberg (Arch. f. Kinderh. 107:216 (Mar. 17) 1936), in the course of necropsies on 232 nurslings, detected 154 with *empyema* of one or several of the accessory sinuses. The incidence of the sinus complications was especially great in the dyspeptic children, and the question arises whether there is an etiologic connection between dyspepsia and empyema of the sinuses. The author suggests that in view of the parenchymatous impairment of the liver existing in the majority of cases of dyspepsia, it may be assumed that, following a coryza, or after another slight cold, empyema of the accessory sinuses develops which, particularly in the cases of otitis media, attacks the adjoining bone. This process is often slow and may cause only slight elevation of temperature. Depending on the duration and severity of the process, impairment of the liver results which, in turn, manifests itself in a digestive disturb-

ance. The author admits that these studies are still inadequate, but stresses that in nurslings a cold or a coryza is not as insignificant a matter as is often assumed, as it may lead to empyema of the maxillary sinus or to disorders of the middle ear. With regard to the treatment of the sinus disorders in nurslings, **short wave therapy** is advised. Moreover in nurslings with dystrophy, treatment of the liver by means of **dextrose** may perhaps prove helpful in addition to the usual measures.

L. Leroux (Ann. d'oto-laryng., p. 415 (Apr.) 1935) discusses *chronic ethmoiditis* in children. He claims that little attention has been paid to this condition and cites a number of cases. In several, the ethmoiditis was associated with asthma. Chronic ethmoiditis usually occurs in the second decade in a child whose tonsils and adenoids have been removed and whose chief complaints are frequent colds and nasal obstruction. The *etiology* is varying. The condition may result from a previous acute coryza, an infectious fever or grip. Usually, the child is disposed to allergic manifestations and suffers from dietary deficiencies, recurring adenoids or a deviated septum. The most characteristic finding is a pale enlargement of the middle turbinate. Polypi are extremely rare. Frequently, there is an associated chronic maxillary sinusitis. The etiologic factors must be taken into consideration in determining the treatment. The author stresses the value of **climatic treatment** rather than dietetic management, which he claims Americans overemphasize. He also believes that the rôle of vitamins has been exaggerated. Locally, he recommends **cauterization of the turbinate with chromic acid** or **removal of its anterior end**. When **polypi** are present, he thinks that it is proper to **remove** them and to **cure** the cells. He is opposed to resection of the

septum because of the difficulties of doing it under general anesthesia and also because he believes that it may affect the subsequent development of the nose.

**ETHMOID SINUS.**—In discussing the problems of the ethmoid, G. M. Coates (Ann. Otol., Rhin. and Laryn. 44:42 (Mar.) 1935) reviews the progress of the conception of *hyperplastic* and *suppurative ethmoiditis*, simple or complicated by allergy, and comments on the value of a *cytologic study* of the secretions. He describes the difference between simple edematous polyp which is allergic, mixed polypoid hyperplasia, and papillary hypertrophy or mulberry polyp. He believes that avitaminosis is an etiologic factor, and recalls Dean's dictum that hypertrophied tonsils and adenoids are frequently the cause of sinusitis in children. Persons with chronic ethmoiditis seek relief (1) because of persistent discharge, bad breath, headache, obstruction, aprosexia, etc., and (2) because they are sent by other physicians who suspect a possible focus of infection as a cause of ocular disturbances, diseases of the gall-bladder, neuritis, etc. The author recommends thorough study and repeated examinations, including displacement with contrast mediums and x-ray examination, before surgical measures are employed. In most cases **conservative nonsurgical measures** will afford relief. If intranasal surgical intervention is required, he suggests preserving the middle turbinate. If extensive disease exists, he recommends the **Sewell** or the **Ferris Smith technique**, and states that care should be taken not to injure the bone, lest the regeneration of the mucosa be delayed. The author quotes Luongo's success in 50 cases in which the constitutional symptoms were cured in 50 per cent. and relieved in 30 per cent.



In a series of 45 cases of *intracranial complications* due to ethmoiditis, C. A. Hutchinson (J. Roy. Army M. Corps 64:235 (Apr.); and 307 (May) 1935) determined that in 19 the complications resulted from the spread of infection *via* the blood stream, in 20 from direct extension of the infection, and in 8 from a combination of both, while in the remainder the route was undetermined. The percentage of such complications in all cases of acute infection was 2.5, and in those of chronic infection, 0.66. In discussing *indications for operation* in cases of chronic infection, the author lays down the following rules:

When the disease is quiescent and is only accidentally discovered by the x-rays, nothing should be done. A patient in good health but with slight catarrhal symptoms is best treated symptomatically. In cases in which the symptoms are so severe as to necessitate operation, the author advises **Mosher's intranasal operation** when the infection is limited to the anterior cells. The anterior end of the turbinate is removed, the cell walls are punched rather than curetted. The author discusses the various approaches, of Coakley, Harmer, Turner and Sewell, that are used in cases in which the infection is mainly limited to the frontal sinus, with obstruction of the duct and involvement of adjacent cells, but he offers no suggestions. He points out the dangers of intranasal approach in cases in which both the anterior and the posterior cells are involved but the frontal sinus is uninvolved and leans to external operation. He favors the **Howarth operation** in cases in which all cells and the frontal sinus are affected. He attributes the persistence of pain after operation either to loculation with impairment of drainage or to hypersensitive mucosa where deep trigeminal nuclei are affected by toxemia.

Failure to obtain cure in cases of frontoethmoiditis is due to (1) insufficient removal of pathologic mucosa, (2) incomplete removal of the cells about the floor of the frontal sinus and the roof of the orbit, (3) imperfect drainage, (4) failure to recognize and treat a crista galli cell of the opposite frontal sinus, (5) hemorrhage preventing adequate view of the field, (6) excessive lavage, or (7) the presence of syphilis, tuberculosis, a foreign body or a sequestrum. Successful treatment may be given by **dry heat, transnasal ionization** and further **drainage** of the ethmoid sinus by the **Mosher method**.

**SPHENOID SINUS.**—H. W. Lyman (Ann. Otol., Rhin. and Laryng. 44:653 (Sept.) 1935) quotes Frazin and Cushing on the failure of operation on the Gasserian ganglion and cervical sympathectomy to bring about relief from *atypical trigeminal neuralgia*, a term used to describe a variety of pathologic conditions which is not true of tic douloureux. Neuralgia emanating from the sphenopalatine ganglion is differentiated from tic douloureux (1) by the history or presence of sinus infection, (2) by the fact that the pain is frequently bilateral, (3) by the tendency of the pain to radiate to the neck and shoulder and (4) by the fact that the pain is more or less continuous and is not inaugurated by stimulation of a trigger zone. In his cases, if relief followed cocaineization of the ganglion, he investigated the posterior sinuses thoroughly and frequently opened and drained them. This procedure was followed by an injection of 5 per cent. **phenol** in 95 per cent. **alcohol**, with relief in 5 cases. One patient had neuralgia of the sphenopalatine ganglion plus a true tic. Relief was obtained from the former by **opening the sphenoid sinus**, but in order to obtain relief from the latter a **posterior root section** was necessary.

**OSTEOMYELITIS OF THE FRONTAL BONE.** — H. P. Mosher (J. A. M. A. 107: 942 (Sept. 19) 1936) discusses osteomyelitis of the frontal bone and reports on 3 cases. He states that the edema of the skin of the forehead is a rough guide to the extent of the bone and periosteal infection. Further, if there is actual bone necrosis, the bone is infected without necrosis for 1 to 1½ inches beyond the necrotic area. Bone necrosis does not occur until 7 to 10 days after the pitting edema appears, and the x-ray is not positive until necrosis appears. Examination of the bone specimen removed in 2 of the cases showed that the infection spreads along the inner surface of the bone, as well as by the diploic veins. When the infection spreads by way of a diploic vein, it may localize at a point far from the original source of infection. When it does so localize, the pus tends to work both inward and outward, giving either a subperiosteal abscess or an extradural abscess, or both, with a destruction of the bone between them. When a case has lasted 2 or 3 weeks, the operator should expect to find one or both of these conditions.

The histologic examination of Mosher's specimens shows in addition that the infection may spread by way of an inner layer of new bone which is formed between the skull and the dura. The small veins which run in the new bone are often infected and there are numerous hemorrhagic clots which also are infected. Further, the infection spreads by way of the fibrous tissue which covers the new bone and which binds the inner surface of the skull to the dura.

The author feels that the **whole face of the frontal bone** should be removed as a routine **from the hairline to the eyebrow**. Preferably, it should be removed in one piece. However, if the

patient is in poor condition and there is an area of necrosis, it is justifiable to work from the necrotic area outward, removing the bone for 1 to 1½ inches in all directions from the necrotic area. He believes further that both **frontal sinuses** should be **opened, and the anterior and posterior walls of each sinus removed**. He feels strongly that the lateral limit of the bone flap on each side should be at least the outer angle of each frontal sinus or, better, the outer angular process of the frontal bone on each side. The objection to this extensive removal is the deformity. It has been proved that fully 90 per cent. of this can be corrected by modern **plastic surgery**.

S. E. Roberts (J. Kansas M. Soc. 36:312 (Aug.) 1935) reports 2 cases of osteomyelitis and abscess of the frontal lobe due to acute frontal sinusitis contracted in a swimming pool during the hot weather of 1934. Both patients were operated on about a month from the onset, and extensive osteomyelitis and a well encapsulated abscess were found. The author made a large skin-periosteum flap, removed the bone widely and drained the abscesses with rubber tubing. These cases demonstrate the value of delayed operation, of good x-ray pictures, and of **radical surgical intervention**. The author believes that bathers who spend too much time in the water lower their resistance and expose themselves to the danger of severe sinus disease.

*Diploic veins* are considered by Wüst (Ztschr. f. Hals-, Nasen- u. Ohrenh. 38: 188, 1935) to be the carriers of infection in cases of acute osteomyelitis, and he notes that the recent literature has been strangely silent on the point of the presence of frequency of these veins. They have been known since Dupuytren's time and were extensively described by Breschet. The caliber of the

venous channels is greater in old than in young persons and is marked by varicose enlargements. The diploic veins may pass across cranial sutures. They are principally without valves and, as a rule, empty into the cranial venous sinuses or else into the foveolæ granulares, where they may anastomose with the vessels of the dura. Wischniewski described a vein frequently found in the frontal bone, which he called *norma temporalis*. Wüst and Prof. Fick, of the Berlin Anatomic Institute, examined 127 macerated skulls and found diploic veins in the frontal bone in all but 21.

### TUMORS OF NOSE AND SINUSES.—

C. F. Geschickter (Am. J. Cancer 24:637 (July) 1935) presents a study of 211 tumors of the nose and sinuses from a total of 2000 specimens removed at the Johns Hopkins Hospital. They were divided as follows: benign epithelial tumors, 19; malignant epithelial tumors, 139; benign connective tissue tumors (exclusive of osteoma), 37; and sarcomas, 16. The various types are described, and typical examples are shown. It is interesting to note that Geschickter found 73 cases of epidermoid carcinoma of the maxillo-ethmoid area, which he calls squamous cell, or transitional cell carcinoma, and 49 cases of lympho-epithelioma. The author points out that the latter were formerly classed with the sarcomas.

**POLYPI.**—A comprehensive study of nasal polypi is presented by L. Leroux (Otorhino-laryng. internat. 19:257 (May) 1935), who divides them into 4 types: (1) solitary sinus polyp, (2) primary ethmoid polyp, (3) diffuse sinus-ethmoid polyp, and (4) deforming polyp of the young. Type 1 is generally known as a *Killian polyp* or a *solitary choanal polyp*. It is unilateral and pedunculated and, as a rule, arises from the antrum by way of the middle

meatus. It frequently gives the impression of acute inflammatory edema of the mucosa. The polypi of type 2 arise from the middle turbinate and vary considerably in size. They are usually unilateral. Removal followed by cauterization, as a rule, effects a cure. The polypi of type 3 are divided into 2 classes: those arising from the ethmoid cells and those originating from other sinuses. They are usually multiple and are accompanied by evidences of catarrhal inflammation. Diagnosis as to the origin is made by means of x-rays and the use of contrast mediums. Therapy depends on the indications. The polypi of type 4 are characterized by widening of the entire nasal structure. Numerous polypi are found arising from all points within the nasal chambers, even including the septum. There is a marked tendency to recurrence after removal, which disappears only after the patient reaches maturity. Nothing new is offered as to the etiology or the pathology. The author notes an increase in the number of eosinophils in cases in which asthma is present. He advises **radical surgical intervention** including thorough **curettage** of the affected sinus mucosa.

**PAPILLOMA.**—An analysis by R. Kramer and M. L. Som (Arch. Otolaryng. 22:22 (July) 1935) of the literature reveals the fact that at least 4 distinctly different types of tumors have been included under the heading of papilloma. These are: 1. *Mucous polypi*, or soft papillomas (Hopmann). The true inflammatory nature of these growths can no longer be questioned, regardless of their epithelial lining. While these polypi are lined most frequently by columnar epithelium, metaplastic changes with transition to squamous epithelium are not uncommon. Such changes are undoubtedly associated with external physical, chemical and inflammatory processes in the nasal chambers.

2. *Innocent cutaneous warts* arising from the vestibule of the nose, especially on the antero-inferior portion of the septum. They are localized, slightly elevated, papillary epithelial hyperplastic lesions surrounded by an area of normal mucosa. They can be removed with ease and show no tendency to recurrence. The literature contains records of numerous instances in which such lesions have been reported erroneously as true papillomas of the nose.

3. *Papillary carcinomas*, which are malignant neoplasms that possess invasive characteristics and tend to metastasize to regional lymph nodes. These tumors are often referred to as malignant papillomas. Although their development on the basis of a true papilloma is a possibility, they should be classified with the carcinomas. Only a small percentage of the growths heretofore reported as papillomas fall into the category of true papillomas.

4. *Papilloma durum* is a true non-malignant neoplasm of epithelial origin and should not be confused with the preceding types. Papilloma durum appears in the form of grayish-red, indurated papilliferous newgrowths, which bleed readily on manipulation. Their hardness is primarily dependent on the marked proliferation of the epithelial tissue. These neoplasms arise from the nasal accessory sinuses and the deeper structures of the nasal cavity. They readily involve a large area of mucous membrane and may attain a huge size. Their tendency to multiple recurrences and malignant transformation is characteristic.

**MUCOCELE.**—Mucocoele of the *maxillary sinus* is a rather infrequent entity, but T. Imai reports 4 cases in which this condition occurred after a radical operation on the antrum, performed some years previously for a condition which was diagnosed as car-

cinoma. Operation disclosed cystic cavities, the walls of which were rich in blood-vessels and lined with epithelium. No glands were present. The growths were firmly adherent in the region of the ostia.

Mucocoele of the *frontal sinus* is more frequent. O. F. Mazzini and M. Cesio (Bol. y. trab. de la Soc. de cir. de Buenos Aires 19:640 (Aug. 14) 1935) describe a case in a man of 60, in which the tumor attained the size of a hen's egg, displacing the bulb downward and outward, and causing headache, somnolence and frontal ataxia. When the mass was opened and evacuated, it left a space which measures 12 cm. anteroposteriorly. The cavity was not curetted for fear of spreading the infection. **Drainage** via the ethmoid cells was instituted at a subsequent operation. A year later the cavity was still draining into the nose.

A. Hartung and T. Wachowski (Am. J. Roentgenol. 34:30 (July) 1935) report 4 cases of mucocoele and call attention to the characteristic x-ray picture, *vis*: enlargement of the sinus, erosion of its walls, increased translucency, displacement of the boundaries of the sinus, distortion of outline and, frequently, reactionary new bone formation.

**OSTEOMA.**—A. Sjöberg (Acta oto-laryng. 23:157 (1935) describes 2 cases affecting the *maxillary sinus*. Statistics from the Sabbatsberg Clinic for the period 1910 to 1934, inclusive, disclosed a total of 1197 major operations on the maxillary sinuses for various conditions, of which only 2 were for the removal of an osteoma. In both cases there were external evidences of the growth, such as swelling of the cheek and obliteration of the nasolabial fold. Suspicion as to the nature of the trouble was aroused through unusual resistance encountered in attempts to puncture the sinus for lavage. X-ray examination,

however, readily outlined the mass, which appeared as a dense, well-defined tumor. In one case the shadow was not of uniform density owing to the spongy nature of the bone. In another case the growth originated in the naso-antral wall, grew into the antrum and by pressure caused a thinning of the orbital and palatal plates. The other tumor grew from both the facial and the oral wall of the sinus. Histologic examination showed newly-formed spongy connective tissue bone and marrow spaces filled partly with connective tissue and partly with fat. The tumors were covered with ciliated epithelium resting on a connective tissue stratum. The author points out that there is considerable difference of opinion as to whether these tumors originate from cartilage rests or from periosteal activity.

T. E. Carmody (Ann. Otol. Rhin. and Laryng. 44:626 (Sept.) 1935) also discusses the theories of the *genesis* of osteoma and adds the following to the 2 theories just mentioned, *viz.*, that the growth originates from the diploe, from ossified polypi or from trauma, and that it is due to syphilis. He summarizes reports of 139 cases collected from the literature, and adds 6 from his own experience. He finds the tumor most frequently in the male and during the period of adolescence. In 2 of his cases it invaded the *maxillary sinus*. One of the patients had a postoperative infection, was reoperated on and died in epileptiform convulsions after the injection of alcohol into the left infra-orbital nerve for relief from pain. The other 4 cases involved the frontal sinus, operation was performed with successful results. In 1 of the cases the infection was extensive, reaching into the orbit and through the posterior wall of the sinus. A pneumatocele was made out in the x-ray picture, and when the tumor was removed there was an escape of air.

As the dura was adherent, it was lacerated, and cerebrospinal fluid escaped. The patient suffered from convulsive seizures intermittently for 3 years but finally recovered.

**ADENOMA.**—Adenoma of the nose and sinuses is extremely rare, but L. Natanson (Acta-oto-laryng. 23:167, 1935) claims to have found 42 recorded cases and reports 1 of his own which he followed for over 10 years. He describes 2 types, a benign growth, which is small, smooth and circumscribed, growing from the septum, the middle turbinate or the posterior end of the vomer; and a highly malignant growth, attaining large proportions and characterized by friability, vascularity and a tendency to recur. This type does not infiltrate until late and rarely metastasizes. The author's patient, a woman of 27, was operated on at least 7 times by the Denker method and later by the Langenbeck method, with recurrences at intervals of from 1 to 2 years, until eventually the orbit and the base of the brain were involved and the patient died of cachexia. Histologic examination of tissue at each operation repeatedly showed a structure that was typically adenomatous, and only toward the end, when the recurrences were more frequent, did the specimens show evidence of malignancy by the presence of epithelial sprouts, mitoses and absence of basilar structure. Prolonged x-ray treatment seemed to make no impression.

**NEURINOMA.**—M. Mittelbach and F. Woletz (Med. Klin. 31:275 (Mar. 1) 1935) report 2 cases of neurinoma of the nose in youths 17 and 25 years of age. Each growth was a large bluish mass. In the first case it filled the nose, antrum and ethmoid cells, and in the other, the nasal cavity alone. The Denker operation was done in the latter case and the Moure in the former. Definite connection with a nerve trunk

was not demonstrated, but histologic examination proved the diagnosis. The examination showed typical parallel placement of the cells, hyalin-like bands of fibers, and a general fibrillary-reticular structure. Silver stains brought out the fibrillary network of the ground substance. The author calls attention to the similarity of structure of *schwannoma* as reported in the American literature.

**CANCER.**—F. L. Lederer (Arch. Phys. Therapy 16:199 (Apr.) 1935) discusses diagnosis and treatment of cancer of the nasal accessory sinuses. He claims that it is not always possible to determine the site of inception of the growth, and therefore the terms "primary" and "secondary" are not dependable. It is better to designate the tumor by the areas involved. X-ray pictures should be studied, particularly for changes in the bony structure. He favors combined **x-ray irradiation** and **surgical diathermy** for the treatment. If radium is available, it is safer to use intracavity contact than **teleradium** because of the danger to the bone by the latter method. Theoretically, therapy depends on the histologic picture of the tumor, but, practically, more can be predicted from the rapidity of its growth, its infiltrative properties and its tendency to metastasis.

In discussing the treatment of malignant disease in the upper jaw, W. D. Harmer (Lancet 1:129 (Jan. 19) 1935) has found that 64 per cent. of all malignant tumors of the *antrum* are carcinomas. The growth is usually very malignant, invades adjacent cavities, and shows a marked tendency to recur after incomplete removal. It rarely metastasizes until late. Twenty-six per cent. of all malignant tumors of the *antrum* are *sarcomas*, and they are usually extremely malignant. The author claims that *endothelioma*, forming 10 per cent.

of the total, is probably allied to carcinoma. The endothelioma grows slowly and tends to recur and metastasize after incomplete removal.

Harmer believes that *removal of tissue for biopsy* may prove dangerous, and he advises doing it with the **endotherm knife** or **preceding it with a small dose of high voltage irradiation**. He advises combined **surgical intervention, diathermy and irradiation** in the treatment and prefers the transcanine or palatal approach. The growth should be thoroughly eradicated, followed by surface application of **radium** about the fiftieth day. The radium needles are placed on a dental plate made of lead to protect the tongue and mouth, and this is first worn for 2 hours night and morning and later for a longer time. The period of treatment covers from 10 to 20 days, with a total of from 1000 to 2000 mg. hrs.

The author reports that 14 of 49 patients with carcinoma are living (6 over 5 years). Two of the patients with light rodent ulcer are living. The results of the treatment of sarcoma were better. Fifteen of 29 patients are living for long periods. Only 2 of 8 patients with endothelioma survived.

G. B. New and C. M. Cabot's (Tr. Am. Laryng. Rhin. and Otol. Soc. 41: 584, 1935) report is most impressive. They give a résumé of 295 cases of tumor of the *maxillary sinus* in which operation was performed prior to January 1, 1929. Ninety-one of the tumors were primary in the *antrum* and 50 were apparently secondary. Forty per cent. of the patients with a primary tumor were without recurrence after 5 years; 72 per cent. of those with primary sarcoma were alive and well after 5 years. A higher percentage of cures (55.6 per cent.) was obtained in the treatment of low grade malignant epithelial tumors

than of the high grade (3 and 4) malignant growths (34.5 per cent.).

Fifty-three per cent. of the persons with a secondary malignant tumor of the antrum were cured for 5 years or more. "These tumors originate in the upper jaw and the prognosis is better than with primary malignant tumors." Of the entire group, *i. e.*, those with primary and those with secondary tumors of different types, 44.9 per cent. were alive and free from recurrence after 5 years.

The procedure described for the *treatment* of these tumors is as follows: **nitrous oxide anesthesia** administered intratracheally, an alveolar or palatal approach, *biopsy* and frozen sections. Tumors of a low grade of malignancy are also attacked with **electrocoagulation**, but more with the idea of establishing drainage and affording access for **radium therapy**. "A protected endotherm point with the spark gap almost closed is used in approaching the more dangerous regions of orbit or ethmoid bone, whereas, a large point with the spark gap well open is employed in regions wherein wide destruction will not be of any serious consequence."

R. Glauner (*Strahlentherapie* 55:195 (Feb. 26) 1936) discusses the desensitization of mucous membrane in protracted fractional x-ray irradiation. The author points out that in the course of protracted fractional x-ray irradiations, particularly in case of *malignant tumors* of the oral cavity, of the pharynx, and of the larynx, there frequently develop reactions in the mucous membrane, which Coutard has called *radiation epithelitis*. In order to reduce this epithelitis, the author sought to achieve a reduction in sensitivity by reduction of the blood perfusion of the tissues by means of painting with an **epinephrine solution** of 1:1000. The anemia thus produced persists for from 30 to 40

minutes or even for 1 hour, *i. e.*, for the duration of the irradiation. In order to demonstrate definitely that the epithelitis could be reduced, the author applied the epinephrine solution only to 1 side. He reports 8 cases of oral carcinoma in which he resorted to the one-sided epinephrinization. In 5 of these cases, the epithelitis was completely suppressed on the side that had been treated with epinephrine; in 2 other cases it was considerably less severe on the treated side; the remaining case cannot be estimated in this connection, since epithelitis did not develop on the treated or on the untreated side.

#### LEONTIASIS OSSEA AND HEREDITARY SYPHILIS.—I.

Scharff (*Monatschr. f. Kinderh.* 65:100 (Mar. 4) 1936) reports the history of a girl aged 11, in whom a hard swelling had appeared on the right superior *maxilla* at the age of 6. The swelling was painless but slowly increased in size. The question arose as to the type of the bone disease. Osteitis fibrosa (Recklinghausen), Paget's disease, and Albers-Schönberg's marble bone disease could be excluded, but the symptomatology resembled that of leontiasis ossea. The author restricts the latter term to a disease entity in which the bone disease is limited to the cranium (more especially to the superior maxilla), leaving the other parts of the skeleton free. Other characteristics are the hardness of the bone process, the onset during early childhood and the painless course. However, even after the disorder had been diagnosed as leontiasis ossea, there still remained the problem of *etiology*. In this connection, the author points out that endocrine disturbances, erysipelas, infectious diseases, fetal defects and trauma could be excluded, but a concurrence with con-

genital syphilis seemed significant, because the literature reports a number of cases of leontiasis ossea in which the Wassermann reaction was positive, and also some in which antisyphilitic treatment had a favorable effect. In the reported case, antisyphilitic treatment was instituted, but although it seemed to arrest further progress, it did not produce a regression and, since the secondary symptoms (difficult nasal breathing) persisted, surgical removal was decided on. In view of the lack of another satisfactory explanation, the author believes that in the reported case the leontiasis ossea suggests an etiologic relation with syphilis.

**RHINOSPORIDIOSIS.**—W. A. E. Karunaratne (J. Path. and Bact. 42: 193 (Jan.) 1936) points out that rhinosporidiosis is a disease seen almost invariably in men, occurring in India, Ceylon and North and South America. It usually affects the nasal cavity, less frequently the conjunctiva, and rarely other sites. It produces a friable polypoid mass that bleeds easily. Only 53 cases have been reported in the literature, although the author has seen 34 instances during the last 13 years. He discusses the structure and life history of *Rhinosporidium* and the morbid anatomy and the histology of the lesion. In the nose, the polyp tends to become obstructive. Often a well marked coryza precedes and accompanies the obstruction. The discharge, which is thin and mucoid and sometimes blood-stained, usually contains both spores and sporangia. Epistaxis is seen in only a few cases, and a definitely purulent discharge is rare. When the growth occurs in the nasopharynx, it may hang downward and cause difficulty in swallowing. In the conjunctiva the tumor readily attracts attention and, in the few cases in which infection of the

lacrimal sac has occurred, obstruction resulted from blocking of the sac by the growth and was accompanied by suppurative dacryocystitis.

A tendency to recurrence is a characteristic feature. The tendency to recurrence would suggest that the parasite undergoes its complete cycle of development in the human body without the intervention of an intermediary host. Another important characteristic is the long history. Tirumurti mentions an instance in which the patient had the infection for 20 years, and in Knowles' case the infection had lasted 16 years. The infection remains localized to the original site, though nearby sites may become infected, but there is no evidence of generalized hematogenic dissemination.

Nothing definite is known about the modes of infection and transmission. As the nose and eye are the commonest sites, it is possible that the organism is transmitted in dust or water. The presence of infection in nearby sites would point to the possibility of autoinoculation. It has not been possible to grow the organism in artificial mediums, with the doubtful exception reported by Ashworth, nor has it been possible to transmit the infection to the lower animals. Infection in farm animals has been observed, and it is possible that there is some definite etiologic relationship between the disease as it occurs in man and in the lower animals.

**RHINOSCLEROMA.**—*Etiology.*—W. G. Drobotjko, S. N. Ruckowsky, S. S. Djacenko and A. Z. Korzinsky (Monatschr. f. Ohrenh. 69: 322 (Mar.) 1935) point out that, according to recent literature, rhinoscleroma is comparatively frequent in Volhynia, in other parts of the Ukraine and in the U. S. S. R. However, in spite of the many newly discovered cases, they are



unable to say whether, as some have asserted, the incidence has increased since the war. They consider it possible that the increased incidence is only apparent in that, as the result of improved clinical and laboratory methods, the number of cases detected is larger. Nevertheless, they concede that rhinoscleroma presents a grave problem in these regions, the more so since the etiology and the epidemiology have not been fully explained as yet.

They report the results of studies which they carried out in 4 villages. They examined the nasal and nasopharyngeal mucus for the presence of capsulated microbes, and they also tried to make the complement-fixation test, according to Bordet and Gengou, with antigen from capsulated organisms, but the latter procedure had to be abandoned. They found that the flora of capsulated microorganisms is rather manifold in patients with rhinoscleroma as well as in those with ozena. They give a tabular report that indicates the individual characteristics of the various types of capsulated bacilli. They observed Frisch's bacillus (*Bacterium rhinoscleromatis*) in a comparatively small number of cases of rhinoscleroma, but they believe that repeated tests might have disclosed it in a number of cases

in which the first test had been negative. But even if they cannot bring definite proof of the etiologic significance of this bacillus, they concede that they found a large number of capsulated bacilli in the nasal secretions of patients with ozena, and they think that this indicates that capsulated bacilli thrive in the pathologically altered mucous membrane of these patients. Studies on children with various pathologic conditions of the nasopharynx indicated the same.

In regard to the *contagiousness* of rhinoscleroma, the authors state that they generally found only 1 case in a family; thus, their studies do not corroborate the assertion of Elbert, Gerkess and Feldmann, who maintained that they frequently found familial foci. Other observers, however, have stated that familial occurrence of rhinoscleroma is rare, and the authors are inclined to agree with them. The authors were unable to detect a connection between *hygienic conditions* and the incidence of rhinoscleroma. They found cases of rhinoscleroma among those who lived under hygienic conditions as well as among those who did not, and they observed it among the well-to-do as well as among the poor. Occupation likewise seemed to have no influence on the incidence of the disorder.

## OTOLOGY

By FRANCIS L. LEDERER, M.D.

**EARACHE.**—Otalgia, pain in or about the ear, may be due to causes other than ear origin. This is significant especially in the presence of a healthy appearing ear.

**Etiology.**—Pain in the ear may be caused by lesions in the teeth, pharynx, larynx, nose and sinuses, less often by intracranial disease. The type of pain is variable as to duration and intensity.

Pain may be referred up to the ear from ulcerative lesions in the pharynx. Tumors may likewise cause pain. Not uncommonly does a sinus suppuration manifest itself solely by earache. Brain tumors and inflammations, particularly in the region of the eighth nerve, may also sometimes cause pain. Lesions of the neck may cause symptoms referable to the ear.

The ear itself may be the seat of a lesion in the external canal, middle ear, Eustachian tube, mastoid process and facial nerve. The anatomic connections and reflex pathways that may be associated with referred aural pain are well known. Many of the areas mentioned may cause reflex stimuli.

The *dental origin* of otalgia with regard to impacted molars and carious teeth has long been recognized. J. B. Costen (J. A. M. A. 107:252 (July 25) 1936) discussed the neuralgias associated with the disturbed function of the temporomandibular joint. This author had previously discussed the same subject of pain and deafness in association with destruction of the mandibular joint. Deductions were based on 125 cases presenting an edentulous mouth and extensive destruction of the joint, producing a wide overclosure of the jaw.

It has been demonstrated by Costen that ear symptoms predominate in patients with edentulous mouths, whose symptoms develop slowly as a pressure effect on Eustachian tubes, and that pain symptoms, with or without herpes of the external canal and buccal mucosa, predominate in the cases of natural malocclusion or malocclusion from loss of molar support on one side only. A few patients with apparently perfect natural teeth were definitely relieved by extension of the joint the very minimal amount of 2 to 4 mm., accomplished by the use of an overlay on the molar teeth. A majority, 89 patients, were above 40 years of age, the largest group being between the ages of 50 and 60 years. Each decade of life results in more wear of the natural teeth or loss of them, with the potential chance of destruction of the mandibular joint.

Some or all of the following symptoms were regularly found associated with these cases of *malocclusion*:

The ear symptoms were intermittent or continuously impaired hearing; stopping or "stuffy" sensation in the ears, marked about meal time; tinnitus, usually "low buzz" in type, less often a snapping noise while chewing; dull or "drawing" pain within the ears, and dizziness, with nystagmus.

The pain and irritative symptoms were headache about the vertex and occiput and behind the ears, typical site of posterior sinus pain, increasing toward the end of the day (atypical sinus history and suggestive of eye headache); burning sensation in the throat, tongue and side of the nose; dry mouth with almost total absence of saliva and, rarely, excessive saliva; occasional herpes of the external ear canal and buccal mucosa, most marked on the edentulous side.

The chief function of the jaw being mastication, it is equipped with powerful muscles, *i. e.*, the masseter, the temporalis, and the pterygoideus internus, all of whose function is to close the jaw. Acting as openers are the factors of the external pterygoid action, the action of the digastric muscle and the natural weights of the jaw. By complicated interaction, the jaw is fixed to aid in the act of swallowing, moves to a varying extent to accommodate the production of speech, and adapts itself to great variations produced by densities of food, yawning, laughter, and so on. The extent of normal opening of the jaw is controlled by the sphenomandibular ligament, the stylomandibular ligament, and the short temporomandibular ligaments making up the capsule of the mandibular joint. The latter being weak at the forward aspect, extreme looseness sometimes permits the condyle to slide entirely beyond the articular eminence, producing subluxation of the jaw. The extent of closure of the jaw is determined by the teeth. Since most of the

power of the muscles of mastication is applied to the posterior third of the jaw, most of the impact of chewing is taken up by the molar teeth, very little being applied in the incisor district, the mandibular joint acting only as a weak hinge or guide to this movement.

It is not surprising, therefore, when molar teeth are missing or the vertical dimension of the jaw is abnormally reduced by shrinkage of the alveolar ridge beneath plates or by grinding away of the natural teeth, that the mandibular joint should assume an unaccustomed burden from this district and much of its structure be destroyed. When this occurs, some of the force is thrown into the incisor region, but most of it is referred upward to the mandibular joint in direct line of the vertical dimension of the jaw. Proper regard for this function is the basis for testing the patient for the mandibular joint "syndrome" and is the basis on which the dentist proceeds to restore the position of the jaw.

The most common symptom observed was *headache*. Sixty-three patients had regular daily headache, more or less severe, 49 of whom described the pain as vertex, occipital and about the ears. Twelve had only supraorbital pain. All presented themselves or were referred for study as sinus cases. Almost all showed more or less sinus infection for which proper treatment was given. Thirteen volunteered the description of pain as increasing toward the end of the day. This was typical of eyestrain headache, and no eye lesions were found. The distribution of pain was quite typical of posterior sinus disease.

The anatomic reasons advanced for the pain are: (1) erosion of the bone of the glenoid or mandibular fossa, and impaction of the condyles against the thin bone, separating them from the dura; (2) irritation by the uncontrolled

movement of the condyles, backward or mesially, of the auriculotemporal nerve, which passes intimate to the mesial side of the capsule between the condyle and the tympanic plate to distribute over the temporal and vertex region; (3) production of reflex pain and sensory disturbance in the various connections of the chorda tympani nerve, the condyle irritating it where it emerges from the tympanic plate at the mesial edge of the glenoid fossa through the petrotympanic fissure.

Reasoning from the fact that the mandibular joint capsule is weaker on the mesial side and the glenoid fossa is protected laterally by the zygoma, Costen assumes that the condyle of the joint most affected would move mesially to impact the nerves, and the condyle of the opposite side would adapt itself downward or forward. The author also assumes that in unilateral loss of teeth the joint on the unsupported side would suffer most destruction. Observation of the jaw movements of this type of case showed that the patient attempts to occlude the remaining teeth by weaving the jaw laterally toward them. The lower teeth slip beyond the upper on occlusion, and the condyle on the unsupported side is pulled mesially and upward by the chewing muscles. Exactly the same thing happens when the natural teeth are worn or badly occluding and fail to take the impact of the chewing movement. The joint on the poorly supported side is destroyed. Its condyle slips mesially on closure, impacts the nerves and initiates pain on the same side.

Glossodynia, pain and sensory disturbances about the lateral pharyngeal wall and tongue (glossopharyngeal neuralgia), and herpes were traced by Costen to an irritation of the chorda tympani and auriculotemporal nerves. The results of reposition of the jaws

were generally good except in a few cases of malocclusion of natural teeth, presenting great difficulty. However, it was noted that the cases showing the best results were corrected in several stages, slowly increasing the vertical dimension of the jaw. This increase in distance is built into the molar district of the jaw and is not merely a problem of "opening the bite." Some failures to obtain a proper result have been traced to lack of understanding of this point and the anatomic problem involved by the dentist.

**NEURALGIA.**—Pain about the face is very often a complaint that brings a patient to seek aid from the dentist, from the otolaryngologist, and sometimes from the ophthalmologist, according to H. Wilkins (J. Oklahoma M. A. 28:327 (Sept.) 1935). The fifth cranial nerve, taking origin from the side of the pons, passes to the middle cranial fossa where the gasserian ganglion is located and from that point fibers pass outward through 3 separate openings to form the 3 divisions. Very often the nature of the pain and local changes in the tissues indicate a peripheral process producing the pain, for example purulent sinusitis, carcinoma of the tongue or an infected tooth. In the absence of signs of sinus infection, dental caries or obvious ocular disease and neoplastic processes, an analysis of the pain should be attempted. A very transient lightning-like pain in one or more divisions initiated by a light touch, a breath of air, a facial movement, attempts to eat, etc., is characteristic of *trigeminal neuralgia* or *tic douloureux*. On the contrary, a neoplasm of the ganglion or a tumor arising from a nearby structure will tend to produce a more continuous pain associated with hyperesthesia or anesthesia. A paralysis or paresis of the muscles of mastication adds further

weight to the diagnosis of a neoplasm of or near the Gasserian ganglion. Tumors arising in the so-called cerebello-pontine angle produce numbness in the fifth nerve distribution. Invading carcinoma from the pharynx may give a picture almost identical with a tumor of the Gasserian ganglion, but careful inspection and possibly studies by biopsy from the nasopharynx establishes the diagnosis.

Since *tic douloureux* involving the glossopharyngeal nerve is frequently unrecognized, W. B. Hoover and J. H. Poppen (J. A. M. A. 107:1015 (Sept. 26) 1936) briefly review the literature in connection with the presentation of 2 cases.

**Symptoms.**—The history and symptomatology of patients suffering from glossopharyngeal neuralgia are all very similar, practically the only variations being the duration of the disease and the frequency and duration of the sharp, shooting or burning pains in the throat. These pains usually become more severe and more frequent with time, but remissions at from a few hours to a number of years are frequently recorded. At the onset, as a rule, the paroxysms are less frequent and may occur only during the day, but as time progresses, sleep is disturbed by nocturnal attacks. The paroxysms of pain are brought on more frequently by swallowing than by any other one thing. However, talking, sneezing, yawning, coughing, laughing, examination of the throat and, in a few cases, manipulation of the ear may bring on an attack. While in pain, the patient may sit transfixed with all muscles tense, or may press his hand against the side of the neck and jaw.

**Differential Diagnosis.**—It is important to give a differential diagnosis between a trigeminal, glossopharyngeal neuralgia and a superior cervical sympathetic pain. A typical major *trigem-*

*inal neuralgia* is a definite clinical entity. It is characterized by paroxysmal attacks of lightning-like pain in the distribution of the fifth nerve, more commonly in its maxillary and mandibular divisions, and is very commonly associated with a point on the face that, when irritated or stroked, will precipitate an attack. This is commonly spoken of as a trigger zone, usually the upper and lower lip at the angle of the mouth. Trigeminal neuralgia is most commonly seen after the fifth decade, although it is occasionally seen in younger people. It is unilateral as a rule, about 0.5 per cent. are bilateral. The point to remember is that it is in the distribution of the fifth cranial nerve. *Glossopharyngeal neuralgia* is a typical paroxysmal attack of pain in the distribution of the ninth cranial nerve. This includes the pharyngeal wall, the tonsillar region, the base of the tongue and, rarely, the ear. In addition, the differential diagnosis between this condition and supernumerary teeth, carcinoma of the lip, carcinoma of the alveolar process of the jaw, and carcinoma of the anterior two-thirds of the tongue must be taken into consideration.

*Trigger areas* of trigeminal neuralgia occur in the buccal mucous membrane and about the lips, nose and various areas on the face. When the first or second divisions of the trigeminal nerve are affected there should be little or no difficulty in the differentiation of these two neuralgias, but when the third division of the trigeminal is involved, a little more care must be exercised to differentiate it from the ninth nerve. In either neuralgia, the pain may seem to spread beyond the distribution of the fifth or ninth nerves, but careful questioning will reveal the point of greatest intensity or the real pain to be in the area supplied by the affected nerve. **Cocainization of the mucous mem-**

**branes** over the distribution of the ninth nerve will, as a rule, temporarily control the paroxysmal pain from this nerve.

**Treatment.**—Medical and surgical treatment are the two methods available in the treatment of *glossopharyngeal neuralgia*. In the author's experience, **trichlorethylene** has been the only drug that has really been efficient in giving a marked amount of relief from this condition. It is administered by the patient's inhaling from 15 to 30 drops from 3 to 4 times a day. The patient is instructed to lie down, drop the required number of drops into a gauze pad or handkerchief, place it over the nose, and inhale the vapor as long as he can smell the trichlorethylene. This inhalation is to be repeated 3 or 4 times a day.

The surgical treatment of choice is the **intracranial section of the ninth nerve** in the posterior fossa. The exposure renders it possible to observe this area for tumors, which occasionally give rise to this neuralgia. Intracranial section prevents the recurrence of symptoms, which is possible following a peripheral section.

According to Hoover and Poppen, an alcohol injection is not feasible, due to the small size of the nerve and because of its proximity to the vagus and hypoglossal nerves and to the jugular.

The **alcohol treatment** of *major trigeminal neuralgia* is advocated by F. C. Grant (J. A. M. A. 107:771 (Sept. 5) 1936) in a report of 185 cases. Many of the cases were of a malignant disease involving the lips, tongue, cheeks, nose or sinuses. The injection of absolute alcohol by the exacting technic described was found to be valuable for relief of pain and for the positive diagnosis of trigeminal neuralgia.

The treatment of neuralgias by **x-rays** is advocated by Coste and his associates (Paris correspondent: *Ibid.*

107:725 (Aug. 29) 1936). Minute doses are employed, usually 75 to 250 r. at a sitting, for a total of 1000 to 2500 r. They feel that exacerbations of pain are objectionable and the dosage should be controlled accordingly.

### THE EAR IN HEAD INJURIES. —HEAD INJURIES AND TEMPORAL BONE INVOLVEMENT.

—T. Skoog (Acta Chir. Scandinav. 77: 383 (Mar. 10) 1936) analyzed 794 injuries of the skull treated at the Surgical University Clinic of Lund, Sweden, between 1924 and 1933. Of these, 370 had a verified *fracture*. The author deals in detail with fractures involving the temporal bone. The *diagnosis* of a fracture of the temporal bone is aided by x-rays far more now than was formerly the case. The percentage of clinically certain or suspected cases of fracture in which the x-ray observation was negative was extremely low in 1933 as compared with conditions in 1924. The surest diagnosis, however, is furnished by the anatomic and functional otologic examination. In 38.9 per cent. of the cases of fracture an involvement of the temporal bone and the auditory organ could be established. The different types of temporal bone fractures are discussed in detail with reference to their symptomatology and prognosis. One may consider the head injuries first as the result of concussion of the brain with ear symptoms and, second, concussion of the brain with concussion of the inner ear. In this division a concussion of the brain can exist without concussion of the inner ear, but the latter cannot exist with concussion of the former.

The *therapeutic measures* in uncomplicated cases run in a strictly conservative direction, stressing careful observation of the cerebrospinal fluid.

**Operation** is recommended at the slightest indication of incipient menin-

gitis. It consists of the chiseling of the mastoid process and exposure of the dura. The radical operation should be resorted to only in exceptional cases. Ninety-four fractures of the temporal bone, comprising 90 pyramidolongitudinal fractures and 4 pyramidotransverse fractures, have been the object of a closer functional otologic examination. The 4 clinically suspected pyramidotransverse fractures exhibited a loss of the cochlear and vestibular functions. Three exhibited a spontaneous nystagmus toward the unaffected side, and in the fourth the nystagmus was not definite, but x-ray study suggested that the fracture involved the labyrinth. Facial palsy occurred in only 1 of the cases and showed some tendency to improvement during hospitalization. The 90 pyramidolongitudinal fractures showed, with 2 exceptions, auditory disturbances of the middle ear as well as the internal ear, though chiefly of the former, and vestibular disturbances in 43.3 per cent. Involvement of the temporal bone does not seem to entail an increased predisposition to disturbances within the vestibular area as compared with fractures of other localization, or in cranial trauma without fracture.

After outlining the symptomatology of *fractures of the cranial base*, H. Loebell (Ztschr. f. Laryng., Rhin., Otol. 26:117 (June) 1935), in discussing the *therapy and prognosis*, points out that involvement of the ear can be demonstrated by a discharge of blood or cerebrospinal fluid from the ear and by examination of the hearing capacity and of the apparatus of equilibrium. Further, he stresses the importance of x-rays of the cranium, according to the method of Stenvers and Schüller, and also bi-temporal x-rays. In doubtful cases, these methods will help in deciding whether the ear is involved and in clarifying the problem of the complicated

fracture. However, the author admits that an x-ray examination which does not disclose a fracture, does not definitely exclude a fracture. After citing the statistics of other observers on the incidence of involvement of the temporal bone, the author discusses the observations he made in 85 cases of fracture of the cranial base. He believes that in uncomplicated cases, whether the ear is closed or open, an expectant attitude is advisable.

In borderline cases of fracture with nonfebrile and painless suppurations (whether the suppurations existed before the accident or developed later), and in which there is practically no inflammation, it is advisable to take an observant and conservative stand. If a suppurating ear is involved in the fracture, if complications, including secondary suppurations, threaten or are present, the complete opening of the spaces of the middle ear with wide exposure of the dura and of possible foci of hemorrhages is the method of choice. When these rules were followed, the author had no fatality from fractures of the cranial base, and he was able to save even patients with severe meningitis who otherwise would probably have died.

In patients with severe injuries, deafness and disturbances in equilibrium may persist, but in the majority, these subside gradually. A definite estimation of the amount of permanent impairment is not possible before at least one year has passed.

Loebell believes that the correctness of his method of treatment of fractures of the cranial base is attested by cases of severest nasopharyngeal hemorrhages, of spontaneous tamponade of the sigmoid sinus, of fracture of the cranial base in the presence of a suppurating cavity, of late meningitis, and of the resumption of flying by 2 gliders who

had sustained fractures of the cranial base.

In discussing the management of head injuries R. A. Money (M. J. Australia 2:810 (Dec. 14) 1935) considers the following pathologic conditions as being covered by the term "head injury": (1) wounds and contusions of the scalp; (2) fractures of the skull and their complications; (3) meningeal and muscular injuries, leading to the various types of intracranial hemorrhage—epidural, subdural, subarachnoid and intracerebral; (4) contusions and lacerations of the brain, with edema and/or hemorrhage, leading to the clinical states of traumatic stupor and traumatic delirium (*i. e.*, concussion, irritation and compression of the brain); and (5) after-effects of any of the foregoing, including mental deterioration, traumatic neurasthenia and fits. A consideration of any large series of head injuries on the basis of traumatic stupor will enable them to be placed in 3 categories, according to their condition on admission to the hospital. They are similarly classed by A. Verbrugghen (Illinois M. J. 69:252 (Mar.) 1936). The first group consists of patients who are deeply unconscious or comatose. These comprise chiefly cases of injury to the base of the skull with rapid and extensive subarchnoid hemorrhages and hemorrhages from the dural sinuses. The patient's condition becomes progressively worse, whatever is done, and death occurs within the first 24 hours and usually within the first 8 hours. In the second group, patients are of 2 main types: (1) Patients who have regained or are already regaining consciousness but are dazed and restless, with immediate retrograde amnesia. Provided a progressive return of the faculties proceeds, the prognosis is good, whatever the injury. (2) Patients who are primarily unconscious but have recovered

and relapsed into a secondary unconsciousness of stupor. Unless careful observations have been made on admission or shortly afterward, it may be difficult to estimate the length of the lucid interval, the depth of this secondary stupor (the crucial point), and the existence of localizing signs. The classic cases of extradural and massive subdural hemorrhage fall into this group, and for them active operative intervention (subtemporal craniectomy, often bilateral) is essential. If the stupor is relatively light and no paralysis is observed, only edema may be present, and recovery may occur spontaneously or by the aid of dehydration methods without major operation.

The *treatment* of acute and chronic cases of cerebral trauma by methods of **dehydration** is fully discussed by T. Fay (Ann. Surg. 101:76 (Jan.) 1935). The third group consists of patients who are stuporous or lightly unconscious on admission and who remain uncoöperative and unresponsive for hours, days or weeks. Despite this lack of cooperation, many useful observations and examinations can be made. The condition of the patients, thus revealed, is gradual and progressive toward recovery; anxiety will be relieved, and there is no need for major surgical intervention. These are usually cases of severer contusions and lacerations. The early adoption of the upright **posture** in a special bed is advocated, and the use of **bromides** and the **barbiturates** for *restlessness* in preference to morphine is urged. The indications for **lumbar puncture**, both diagnostic and therapeutic, and the administration of **hypertonic solutions** are stated. The routine use of a simple **spinal glass manometer** to determine accurately the intracranial tension before deciding on active therapeutic measures is advised. The repair of defects in the cranial vault by

**bone grafts** from the ilium is advocated. Failure of compensation and the onset of compression call for operation. **Subtemporal decompression** is usually sufficient to enable evacuation of the clot. Early **evacuation of localized intracerebral hemorrhage** to prevent the onset of fits is advocated.

**AURAL VERTIGO.**—Vertigo or dizziness is comprehensively discussed by T. G. Wails (J. Oklahoma M. A. 28: 418 (Nov.) 1935), who reviews the physiology of the vestibular apparatus and classes the abnormal functioning as due to excitation or depression. These may be due to intoxication, disturbances of circulation, reflex stimulation or trauma.

Mild intoxications or actual inflammation may be due to absorption from a sluggish bowel, rather than being reflex in origin. It is termed "biliousness." Mild disturbances also may result from alcohol and tobacco. An alcoholic staggers because he has an intoxication of either the end organs, pathway or cortical representation of the vestibular apparatus and cannot compute his position. He feels that he is standing erect and the ground is moving up to him, instead of him moving toward the ground.

Focal infection from a number of sources may cause mild symptoms. Acute toxemias from influenza may cause a labyrinthitis with violent symptoms which, however, usually clear up in a few days as the amount of absorption decreases. The inflammation may be so localized as not to affect the hearing, but generally it spreads to the rest of the end organ and the hearing becomes impaired. The part played by focal infection in the production of aural vertigo is discussed by W. G. Shemeley, Jr. (Eye, Ear, Nose and Throat Monthly 14:380 (Dec.) 1935).



Violent intoxications such as produced by syphilis, mumps, epidemic meningitis, and tuberculosis may cause a neuritis of the eighth nerve that will completely destroy both functions.

Since the fibers of both divisions are so closely associated in the main nerve trunk, it is impossible to cause trauma in such a way that both functions will not be proportionately impaired. The nerve completely fills the Fallopian canal, so that it is impossible to fracture the bone without tearing the nerve. When the mastoid is fractured, either no loss or complete loss is suffered. There may be a conduction deafness due to blood or rupture of the drum. This usually clears up with time and depends upon keeping out infection.

Dysfunction due to circulatory disturbances such as fainting, embolism, thrombosis, edema, ischemia, and hemorrhage may produce vertigo. The treatment, of course, is to find the high blood-pressure, anemia, nephritis or general disease causing the symptoms. Ménière's syndrome is a well known example. The symptoms are violent because of their sudden onset.

Vertigo or nystagmus developing in the presence of an ear infection is always a serious symptom. It means either stimulation or invasion of the labyrinth or its pathways. There may be first only an irritation of a canal due to erosion of the bone with stimulation of the membranous labyrinth, or there may be actual invasion of the canal by living organisms. Labyrinthitis may exist as serous or purulent, and may be circumscribed or diffuse.

The most valuable aids in the *diagnosis* of aural vertigo (neuro labyrinthitis) as the result of focal infection are summarized by Shemeley (*Ibid.*) as follows:

1. A complete differential blood count. At the same time a test for possible lues

should be made, since syphilis frequently simulates focal infection.

2. Functional hearing tests, carefully made.

3. A search for spontaneous rhythmic nystagmus.

4. The making of the galvanic tests.

5. The observation of the duration of the after-turning reaction.

A greater degree of loss of function on the affected side will be shown by cases during the height of an attack than will be found during the period of recovery or during the period following the thorough removal of the exciting focus.

To sum up the part played by focal infection in the production of aural vertigo (neuro labyrinthitis) is to discover that it is the most frequent etiological factor, and that such vertigo (aural) generally results from an unilateral neuro labyrinthitis.

Clinicians have discovered that aural vertigo resulting from focal infection is much more common than the average otologist would suppose, in fact, focal infection is the most frequent, though too often, unrecognized cause.

A. A. Cinelli (*Laryngoscope* 46:64 (Jan.) 1936) finds vertigo a complex problem. He states that unless there is a coördinated, chronologic procedure of examination, the problem may be delegated to the realm of mysticism. He considers the vertigo associated with aural lesions, with central nervous system lesions, ocular lesions and systemic lesions. Equilibrium depends upon 3 senses: (a) kinetic static; (b) ocular; (c) kinesthetic. Systematized or tactile forms of vertigo, *per se*, are of no clinical value. Pathological factors producing vertigo are: (a) inflammation; (b) hyperemia; (c) ischemia; (d) faulty water metabolism; (e) pressure; (f) reflex phenomenon. Vertigo is essentially an ear problem. Ninety per cent.

of cases are due to dural lesions. Peripheral vertigo in many cases may be differentiated from central vertigo.

**MASTOIDITIS.**—Acute mastoiditis, including indications for operation, is discussed by I. D. Kelley, Jr. (J. Missouri M. A. 33:137 (Apr.) 1936). While mastoiditis is seen in all periods of life, each period has its own peculiar type of ear trouble. To appreciate fully the clinical problems of mastoiditis in childhood, the anatomic differences between the temporal bone of the child and that of the adult must be clearly borne in mind. Since there is no mastoid process in an infant and no mastoid cells in a young child to conceal a dangerous focus of infection, a more tolerant attitude in dealing with a persistent elevation of temperature in a young child should be taken than might be safe to follow in an older person with a fully developed mastoid. Many observers feel that in infants with middle ear and mastoid infection, the gastrointestinal and general symptoms are quite characteristic, and that if the symptoms do not subside after a myringotomy, a mastoidectomy should be done.

As the mastoid process develops and the problems of mastoid diagnosis and operative technic multiply, no hard and fast rules can be devised either for the necessity of an operation or for the opportune time to perform it. Each case presents an individual problem. The pathological conditions present at the time of examination should be visualized from a study of the whole picture, and the surgeon should not be deceived by any of the findings including the x-ray; but should wait for any reasonable chance for the mastoid inflammation to become localized before operating. Final decision depends on clinical experience, judgment, and sometimes intuition.

The weak point in the treatment of mastoiditis by surgical drainage is the lack of assurance that the operator has reached all the infected cells in the mastoid about the ear and in the petrous bone. When mastoidectomy is followed by a chronic purulent otitis media, it must be explained by a lack of complete cellular drainage either in the mastoid or adjacent structures, and the surgeon should be on the alert for symptoms and signs of a petrositis. Decision as to the opportune time to perform a mastoidectomy is of the utmost importance. This requires the keenest judgment and, when rightly exercised, lessens the possibility of needless operation, reduces the number of complications, and paves the way for a smooth convalescence. A comparison of the number of complications occurring spontaneously during the first few days of a mastoiditis with those which follow mastoidectomy performed in the first few days of an infected mastoid would show a greater number in the cases operated on. However, where there is a history of repeated mastoid involvement, the more recent the previous attack, the earlier is operation justified.

Cavazzutti (Semana méd. 43:928 (Oct. 1) 1936) states that from the first days of acute suppurative otitis media a mastoid reaction takes place. According to local and general factors, the mastoid reaction may regress within a week or become more intensified as mastoiditis complicates otitis. In the latter case, mastoiditis completely develops in 21 days. The *diagnosis* of mastoiditis is made by the persistence and intensifications of the symptoms of the mastoid reaction after the first week; external inflammation in the mastoid region (differentiated from the early mastoid reaction by the time of appearance of the inflammation in relation to

the duration of the disease); persistence of deep arterial pulsation (which indicates the persistence of empyema); persistence of neuralgic pain irradiated to the corresponding trigeminal territory; lowering of the posterior superior wall of the external auditory canal and destruction of the mastoid bone, verified by x-ray examination of the bone. Fever, especially if high, beyond the first week is an unfavorable symptom which, alone or with other symptoms, may indicate an operation.

Operation must be performed in all cases of acute mastoiditis in which the diagnosis is confirmed, but especially in mastoiditis complicated by subcutaneous abscess of the mastoid region and otitis of 3 weeks' duration with inflammation of the surface of the apophysis, or without apophyseal inflammation but with subjective and objective symptoms of an unfavorable evolution and no tendency to a regression of the disease. Grave complications, whether or not fully developed, indicate immediate operation, regardless of the duration of the disease. Systematic performance of an operation during the first week of otitis to prevent the development of mastoiditis is inadvisable. *Indications for operation* during the first and second weeks depend on the evolution of the disease and the development of grave complications. All cases of otitis the evolution of which is not favorably modified by the fourth week, are indications for an immediate operation, regardless of the absence of alarming symptoms. In cases in which the diagnosis is already confirmed but in which there are doubts as to the advisability of operating, the decision is based on the following principle: Operation for mastoiditis which could evolve satisfactorily without surgical intervention is better than losing patients who might have been saved by it.

Mastoiditis in *malnourished infants* is discussed by C. H. Hall (J. Oklahoma M. A. 29: 247 (July) 1936), who states that most of the cases are admitted to the hospital primarily for the treatment of a subacute or chronic diarrhea. Usually, there is a history of poor feeding associated with poor hygiene and home conditions. Many of the cases give no history of symptoms pointing to involvement of the middle ear or mastoid. The author quotes certain authorities who have dealt with this problem and have at different times committed themselves as to their views. As regards the subject of *treatment*, Hall states that it is sometimes difficult to convince the otologist that there is a mastoid infection and to get him to carry out the rather simple surgical procedure indicated. The operation is done under local anesthesia and consists of an **antrotomy**. Extensive cleaning out of the mastoid should be avoided, as in these patients the general condition is not good and they are poor risks for extensive surgical work. If the simple antrotomy is done, it takes very little time and there is little if any postoperative shock. As the general condition of the patient is very important, usually several **blood transfusions** are needed.

Recovery, if it takes place, is not as a rule rapid in these cases and may be a matter of weeks. Very often there are many ups and downs. Every infant with this condition should be given the benefit of the doubt and operated. There is very little chance of recovery if the mastoid is not drained.

**OTOGENIC COMPLICATIONS.**—Neurologic complications of *acute* and *chronic mastoiditis* are presented by C. H. Bayha (Ohio State M. J. 32: 417 (May) 1936). In a series of 106 cases of mastoiditis without intra-

cranial extension, Nielsen and Courville found alterations in the deep reflexes, headache, eye ground changes, or pathological reflexes in over one-half of their cases. With an appreciation of these possible findings in mind, the position of a neurologist who is called in consultation on a case of mastoiditis with suspected intracranial extension, is a difficult one.

A number of factors enter into the question of whether or not a given patient will have an intracranial complication with the mastoiditis. The chief of these factors are: (1) the age of the patient, it being well known that very young children seldom have mastoiditis, due probably to underdevelopment of the mastoid cells; (2) the virulence of the infection, some infections being so virulent apparently that no successful fight can be made to wall off the infection, and it goes on to a terminal meningitis or encephalitis; (3) the resistance of the individual; (4) last, but not least, the skill with which the problem is handled by the attending physician.

The symptoms by which lateral sinus thrombosis manifest themselves can be readily divided into 2 general groups: (1) the systemic and (2) local. Because of anatomical reasons, the right lateral sinus is more frequently affected than the left, and because of the cerebral congestion, dizziness, nausea, and vomiting may be encountered. By ligation of the internal jugular vein with evacuation of the infected clot, the infected material is obviously shut off from the general circulation. The patients who fail to recover from lateral thrombosis die either from the general sepsis with metastatic abscesses in various organs or of meningitis.

If the infection is confined outside of the dura, a condition of so-called sterile *meningitis* is set up. When the infection

penetrates the brain coverings and becomes a diffuse subarchnoid inflammation, the case becomes virtually hopeless. If the cells in the tip of the petrous portion of the temporal bone become involved in the infection, a circumscribed area of *leptomeningitis* may be set up. *Brain abscess* from otic infection may arise either in the temporal lobe or the cerebellum, usually the former. The stage of localized encephalitis may last several weeks, and during this period high temperature, chills, and evidence of systemic infection are present. If the infection remains localized and encapsulation occurs, a latent period of several weeks is generally seen. In the *cerebellar abscesses*, ataxia, usually of the same side, nystagmus toward the side of the lesion, severe occipital headache and stiff neck, associated with a fairly high degree of choked disc usually are sufficient to make the diagnosis. Intracranial complications of otitic infection are fairly uncommon, occurring in 10 per cent. or less of the total cases seen.

**Meningitis.**—*Benign Aseptic Suppurating Meningitis.*—E. Glanzmann and D. Heller (Schweiz. med. Wchnshr. 66: 541 (June 6) 1936) call attention to the fact that there are entirely benign serous and even suppurating meningitides, and that for this reason it is advisable to be cautious in rendering an unfavorable prognosis in cases presenting meningitic symptoms. There is an acute onset with meningitic symptoms. The spinal fluid shows meningitic changes, *i. e.*, there may be a slight increase in the mononuclear cell elements, while the fluid remains clear (serous meningitis), or there may be a noticeable suppurating turbidity. Direct examination as well as the culture method reveal that the cerebrospinal fluid is sterile (aseptic meningitis). The course is relatively short, benign, and without secondary

complications. Etiologic factors in the form of local disorders (otitis, sinusitis, pneumonia, intoxication) or in the form of systemic diseases (acute or chronic infectious diseases) are absent. After reporting the clinical histories of 5 cases of their own observation, the authors point out that aseptic meningitis develops chiefly in children and occasionally even in nurslings. They discuss in detail the symptomatology, the hematologic aspects, the clinical course, the differential diagnosis and the therapy. With regard to the latter factor, they say that for diagnostic as well as for therapeutic reasons repeated **spinal punctures** are advisable, for these often effect a reduction in fever and rapid cure. They also prescribe **methenamine** and **aminopyrine**. In the most refractory case, they resorted to the intravenous injection of a **bacterial protein preparation**. In order to avoid collapse, it is advisable to administer **caffeine** or other **cardiac stimulants**.

*Otogenic Meningitis.*—Of H. Bjork's (Finska läk.-sällsk. handl. 79:304 (Apr.) 1936) 29 cases of otogenic meningitis in acute otitis in which treatment was administered from 1930 to 1935, 16 represented primary and 13 secondary meningitis. Of the former, 13 were tympanogenic (4 fatal) and 3 labyrinthogenic (2 fatal). Of the latter, 11 resulted from sinus thrombus (6 fatal) and 2 from brain abscess (both fatal). Of the 14 deaths, 2 were caused by other complications, the mortality from meningitis was thus 44.4 per cent. The 9 cases in which there were bacteria (Streptococci) in the cerebrospinal fluid were all fatal. The author concludes that meningitis in connection with acute otitis originates equally often from primary and from secondary infections. The great majority of cases are due to a tympanogenic or a sinusogenic infection. Disturbances in development play

an important part in the progression of the disorder to the meninges; in 26 of his 29 cases there was an abnormally wide or an obstructed pneumatization.

By far the greatest problem of otologists is meningitis, according to the report of the New York Committee on otitic meningitis (Arch. Otolaryng. 24: 680 (Nov.) 1936) presented by J. G. Dwyer. Ninety-seven per cent. of persons with meningitis die. The Committee is trying to get ahead with the problem. Since the last report in New York, there have been 22 cases, with 1 recovery. The Committee has met regularly to analyze the different cases. It is believed that in the last 1½ years, 4 lives have been saved by one of the points that the Committee has been stressing, namely, that a cloudy fluid without organisms means that one should operate and find the focus.

The work at present is purely educational. The Committee is not attempting anything in the way of treatment because resources are limited, but it is believed that tremendous help may be gotten in the early *diagnosis* of meningitis by the recognition of 3 simple factors: the blood count, the chemistry of the spinal fluid, and the pathways of infection. When a patient dies of mastoiditis, the members of the Committee attempt to analyze some error in technic. From postmortem examinations and other observations and analysis of the histories, most deaths ascribed to mastoiditis are practically from bacterial invasion from the nose and throat. The number of deaths due to injury or exposure of the dura is small. Several autopsy specimens prove the pathway from the sphenoid sinus. Six specimens from patients on whom partial autopsy was done prove that there was essentially an osteomyelitic process and not mastoiditis. These patients were lost from the start,

When there is a persistently high *blood count* in an adult—from 30,000 to 35,000—with involvement of the mastoid or the ear, and when involvement of the chest is excluded as a cause, meningitis will develop. One may find out from this blood count 4 or 5 days or a week in advance and be prepared.

As to the question of *cloudy fluid*, the point is emphasized that a persistently cloudy fluid, loaded with cells but with no organisms, indicates that the patient can be saved. If there is too much delay, meningitis will develop.

The routine which A. Lewy follows at the Cook County Hospital of Chicago, is that when a patient is admitted with a presumptive clinical diagnosis of meningitis, if the spinal fluid is found to be cloudy, he is given the **antimeningococci antitoxin intravenously**. Some excellent results, superior to those ordinarily obtained by the intraspinal use of the antimeningococcic serum have recently been reported. This is done whether there is an associated running ear or not. However, if there is an associated running ear and the diagnosis of meningococcic meningitis is not positively established, in the presence of a cloudy spinal fluid and clinical evidence of meningitis, they immediately proceed to **operate** on the mastoid in order to uncover the dura in the middle and posterior fossa, without awaiting the result of culture. Lewy believes that they have saved most meningitis patients with cloudy fluid who had no viable organisms in the spinal fluid. If the organisms were found simply on smears, that did not discourage them. Some such patients, also recovered. They rarely saved a patient whose spinal fluid showed a positive culture. According to Lewy, the crux of the situation, so far as the prognosis is concerned, is whether or not there are viable organisms in the spinal fluid.

**Lateral Sinus Thrombosis.**—In a series of 26 cases, W. S. Snyder (Kentucky M. J. 33:360 (Aug.) 1935) found that the incidence of the disease varies with age and sex to the same degree as does mastoiditis.

It is most common in acute cases, where there is generally a combination of virulent infection with lowered bodily resistance. In chronic cases there is generally an acute virulent infection superimposed upon an old chronic process. Spread of the disease from the mastoid cells to the lateral sinus is either by direct extension or an extending thrombophlebitis along the smaller blood vessels. The development of thrombosis is often subsequent to the mastoidectomy. Among 26 cases, the thrombus was found at the time of the mastoidectomy in only 9 instances.

As to *symptoms*, the temperature is intermittent, varying from subnormal to chills and fever. When the patient is free of fever, there are practically no subjective symptoms. Persistent unilateral headache, not relieved by analgesics, is very suggestive. There may be localized edema, due to the stasis of the blood caused by thrombosis of the lateral sinus. In coöperative patients, the *Tobey-Ayer spinal manometer test* is positive where there is complete occlusion of one of the sinuses.

Blood cultures, where positive, are very suggestive. A negative culture, however, is of no value. In this series, 45.4 per cent. gave positive blood cultures. The *streptococcus hemolyticus* is by far the most likely organism to be found. Mastoid cultures are of value only in that by them the type of infecting organism may be found. Examination of the blood demonstrated the extent of the pyemia and the resistance of the body.

Whether the jugular be ligated before or after the sinus is opened depends

upon the circumstances in each individual case. In Snyder's series of cases, the time of ligation of the jugular did not affect the results. When the sinus has been laid bare, the *diagnosis* of thrombophlebitis may be made (1) by the presence of pus passing from the sinus, (2) by palpation of the hard clot within its walls, and (3) by its appearance. If the diagnosis is in doubt, an exploring needle may be used or the sinus laid open with a knife.

The postoperative course varied greatly. The temperature fell to normal in a few days in the most favorable cases, but it varied from 1 to 51 days. Complications occurred in 65.3 per cent. of this series of cases. They were of 2 kinds: (a) Those resulting from direct extension of the infected sinus; and (b) those caused by bacteria disseminated by the blood stream. In this series of cases 46.1 per cent. died. The average death rate as reported by various clinicians is about 45 per cent.

In a preliminary study of 100 consecutive routine x-rays of the occipital bones of normal persons taken in the anteroposterior projection plane, P. Woodhall and A. E. Seeds (Arch. Surg. 33:867 (Nov.) 1936) demonstrated relative differences and variations in the size of the bony markings of the lateral sinuses that closely correspond to the anatomic observations previously reported. This normal standard of variation, appraised by x-ray study, is of clinical value in determining the significance of irregularities obtained by the Queckenstedt test and in determining the dynamics of the venous return from the brain in the presence of thrombosis of the lateral sinus or the jugular vein.

C. M. Anderson (Proc. Staff Meet. Mayo Clin. 10:785 (Dec. 11) 1935) reports a case of mastoiditis in which the particular points of interest in the diagnosis were entirely negative blood

cultures, the lack of subjective symptoms, the presence of choked discs, the marked lowering of the fever after the first operation, and the continued nausea and vomiting with listlessness. The negative blood cultures probably could be accounted for by the walling off of the abscess in the vein by a clot below the point of infection. Exposure of the sinus allowed the phlebitis to subside sufficiently to produce a drop in the fever. The choked discs, which are usually interpreted as indicating intracranial pressure could have been caused by the interference with the return circulation from the brain until sufficient collateral circulation was established. The listlessness and nausea of the patient seemed to be caused by the abscess contained within the sinus. In Anderson's opinion, the *Tobey-Ayer test* has proved a reliable one, although some investigators have found that it is about 20 per cent. less accurate on the left side. This probably is attributable to the variation in the origin of the lateral sinus in the region of the torcular Herophili. However, any laboratory test that will be reasonably correct 4 out of 5 times is worth while.

H. L. Williams (*Ibid.* 11:214 (Apr. 1) 1936) reports a case of sinus thrombosis with papilledema and signs of meningeal irritation as follows:

A girl, 5 years of age, came to the clinic with a history of recurring attacks of acute otitis media almost from birth. Four weeks before her admission to the clinic she had bilateral acute otitis media, with spontaneous rupture of the ear drums and drainage. From the right ear, drainage stopped after 3 or 4 days, but from the left ear it continued. Following an attempt at washing out the ear by syringe, a severe headache on the right side, tenderness over the left mastoid process, and a high septic type of temperature developed. Mastoidectomy was advised and performed elsewhere. At operation, the disease was found to involve the sigmoid sinus on the left side, and in attempting to uncover it, the sinus was

opened. Because of the severe hemorrhage, the operation was not completed. Five days later, when removal of the pack from the sinus was attempted, bleeding recurred. The patient was then referred to the clinic for care.

Williams packed off the sinus above and below and completed operation on the mastoid. The fifth day after operation, the patient's temperature rose to 105° F. (40.5° C.) She continued to have a septic type of temperature with gradual rise of the crests until the eighth day, when the temperature was 106° F. (41.1° C.) and rigidity of the neck, graded 2 plus, appeared. Kernig's sign, grade 1 plus, and bilateral choked discs of 1 diopter were present. Spinal puncture was performed. The fluid was found to be under normal pressure and contained 1 lymphocyte per c.mm.

The mastoid wound was reopened and the sinus uncovered about half-way back to the torcular Herophili and down almost to the jugular bulb. There was free bleeding from the torcular end of the sinus but bleeding from the bulbar end could not be induced, although a suction cannula was thrust into the bulb itself. The part of the vein not opened at the previous operation was slit up and the free edges were cut away. The jugular vein was then ligated in the neck. The day following the operation, the stiff neck and Kernig's sign had disappeared and on the second day the temperature reached normal. The choked discs subsided until at present (March 11) there is no evidence of papilledema on the left side and less than 1 diopter on the right.

According to Williams, the associated symptoms of meningeal irritation in this case are difficult to explain pathologically. In a small percentage of cases, one sigmoid sinus or the other may be absent or may be so small that it does not transmit enough blood to keep the intracerebral circulation functioning normally. At the first operation there was no involvement of the jugular bulb and it is possible that extension of the thrombus to the bulb could have caused a sudden increase in the intracerebral pressure with the production of the signs noted. Evidence against such an etiology is the fact that even in cases of cavernous sinus thrombosis, with marked interference with the venous drainage

from the orbit, papilledema is not often seen. However, blood which drains from the orbit sometimes does not go through the cerebral circulation at all, or at least only in part, for the inferior ophthalmic vein frequently joins the pterygoid plexus. Since there must have been an anomalous arrangement to produce the unusual signs in this case, the conditions may have been such that interference with the cerebral circulation could produce these signs. Evidence against localized meningo-encephalitis being the cause of the signs in this case is the fact that the spinal fluid was completely negative, whereas even in cases in which the spinal fluid is sterile and the irritation is from probable toxic absorption, an increased spinal fluid pressure and increased cell count are found. Williams prefers to attribute the symptoms to the thrombus advancing to the jugular bulb and closing off completely venous drainage through the right jugular foramen. This advance of a thrombus is somewhat contrary to the recent theoretical work of Dixon, who has endeavored to demonstrate that a thrombus proceeds only against the direction of the blood current. However, in this case, the jugular bulb was not shut off at the time of the first investigation of the sigmoid sinus. In a vein in which phlebitis has involved the wall, there is no reason to suppose that the advance of phlebitis down the wall of the vein would not result in a thrombus which advances in the direction of the blood current.

Thrombosis of the lateral sinus and jugular bulb of nonotitic origin with a new diagnostic sign is reported by S. Karelitz (Am. J. Dis. Child. 51:1349 (June) 1936). The *diagnosis* and mode of development of thrombophlebitis of the lateral sinus are usually fairly clear. A septic temperature and chills in the course of purulent otitis media, with or



without evidence of mastoiditis, suggest thrombosis either of the lateral sinus or of the jugular bulb. Positive results of blood cultures are of great significance and usually indicate imperative operative treatment of all such cases. The otitic infection is the origin of all such cases.

Retrograde thrombophlebitis of the jugular bulb and the lateral sinus may occur and can be recognized clinically. In 2 cases it was secondary to thrombophlebitis of the internal jugular vein and in the third to a retrograde spread from the diseased left lateral sinus to the healthy right lateral sinus and jugular bulb.

A new finding is described which consists of painless involvement of the ear; bluish or dark bluish-red engorgement of the drum, starting at the periphery and gradually involving the entire drum and even the adjacent parts of the canal wall; persistence of good hearing; absence of changes in the canal wall other than that of congestion, and absence of signs of involvement of the mastoid, except possibly slight tenderness due to congestion. This picture, either with or without simultaneous involvement of the cervical glands of the same side, should suggest the presence of thrombosis of the jugular bulb or of the lateral sinus or both. When chills, a septic temperature, and positive results of blood culture for hemolytic streptococci are observed along with the otitic findings, surgical exploration of the sinuses of the affected side is indicated.

Karelitz later learned of 6 more cases of retrograde thrombophlebitis of the lateral sinus and jugular bulb. In 2 of these cases the condition was diagnosed at autopsy, and in the other 4, a diagnosis was made clinically. In the 4 cases in which a clinical diagnosis was made, there was a history of acute pharyngitis, cervical suppuration (probably of broken-down glands in the region

of the internal jugular vein) and bacteremia. In 2 of these cases, otitic engorgement was noted; in the other 2, the condition of the ear was not noted, the correct diagnosis having been suggested by the finding of thrombophlebitis of the internal jugular vein on operation for the cervical suppuration.

**Brain Abscess.**—J. E. J. King (Ann. Surg. 103: 647 (May) 1936) describes his method for the operation of brain abscess by open approach to the abscess, removal of the overlying cortex and a portion of the presenting capsule, evacuation and irrigation of the abscess cavity, thorough inspection of the cavity, and its "eventual obliteration" by temporary eversion and herniation. Most of the brain abscesses in which this treatment is employed are secondary to infection of the middle ear and mastoid or of the nasal sinuses, or the result of trauma. This method is not indicated in cerebellar abscess or in small, deep and centrally located cerebral abscess. The vast majority of all cerebral abscesses, the author has found, "approach the dura at a point where it can be attacked at a depth which varies from  $\frac{1}{2}$  to about 3 cm." The overlying brain substance is removed by means of the electrosurgical unit; the author has never seen any permanent sequelæ such as aphasia, mental deterioration, or paralysis result from this procedure. The abscess capsule is opened with the electrosurgical needle and the pus removed by suction. No drainage tubes are used but the abscess cavity is packed with iodoform gauze strips; a small rubber irrigating tube is carried within the overlying gauze and instillation of azochloramid solution is made into the superficial dressing every 2 hours. **Azochloramid** has been found superior to Dakin's solution because more prolonged in action, nonirritating to the skin (or scalp), and easily prepared. At daily dressings, the

iodoform gauze strips are gradually removed until the floor of the abscess cavity becomes sufficiently elevated to permit the complete removal of the gauze within the cavity. The floor of the cavity is not allowed to become elevated beyond the level of the skull; lumbar puncture may be used by the third or fourth postoperative day to prevent further herniation. In 17 cases of single brain abscess in which this operation has been done, there were 3 deaths, a mortality of 17.5 per cent.; in the last 10 cases there was only 1 death.

In a symposium on *cerebellar abscesses* at the annual meeting in April, 1936, of the French Otoneuro-Ophthalmologic Congress, papers were read by Ramadier and Caussee (otologists), Andre-Thomas and Barre (neurologists), and Velter (ophthalmologist). Abscess of the cerebellum most frequently occurs in cases of chronic otitis media. There are *symptoms* that are of value in localizing the seat of the infection. For example, bradycardia is far more marked in cerebellar than in cerebral abscess. The headache is typical also, being occipital. The neck rigidity stands out in most cases in contrast with the complete absence of the Kernig sign.

Choked disc is more common in cerebellar abscess than optic neuritis, the reverse being true of cerebral abscess. The loss of muscle tonus on the same side of the body as that on which the abscess is situated is an early sign that should always be looked for. The evidences of vestibular disturbance are of almost equal value to the cerebellar symptoms themselves. Spontaneous nystagmus is especially frequently observed. Death from respiratory paralysis is not uncommon.

Many cases are not diagnosed because the clinical signs are atypical. In a small number of patients the symptoms

are manifold and diagnosis is not difficult. In others, some complications, such as diffuse meningitis, thrombophlebitis or labyrinthitis, obscures the underlying condition or the patient is seen in a comatose condition.

The **operation** should be done in 2 steps. In the first, the overlying bony structures are removed. Much information as to the existence of vascular or meningeal complications is thus obtained. After an interval of from 24 to 48 hours, the second step is undertaken to drain the abscess.

The *prognosis* even in cases in which operation is performed is unfavorable, the mortality varying from 70 to 75 per cent. because of the difficulty of finding the abscess even when diagnosed, and the fact that even drainage does not prevent the appearance of such a complication as encephalitis or meningitis.

**Facial Paralysis.**—The appearance of a facial paralysis in the course of a suppuration of the middle ear is always to be regarded as a serious symptom, according to C. Hirsch (New York State J. Med. 36:430 (Mar. 15) 1936).

If the onset of a facial paralysis in an acute otitis media occurs in the very first days of the inflammation of the middle ear, such a facial paralysis, contrary to the teachings laid down in so many textbooks and handbooks, does not, as a rule, indicate a mastoidectomy. Only in the event that such a facial paralysis does not clear up in the course of 2 weeks or so after an extensive myringotomy, or if other symptoms arise, it may well become an indication for a **mastoidectomy**. If a facial paralysis develops in the course of an acute purulent otitis media in the third or fourth week, it may have been caused by a lingering mastoiditis and may be an indication for a mastoidectomy.

Facial paralysis arising in a chronic purulent otitis media without cholestea-

toma may clear up without any operation. If other reasons for a radical operation exist, facial paralysis may be a weighty contributory indication for an operation. Facial paralysis in a chronic purulent otitis media with cholesteatoma is an indication for an immediate radical operation.

Facial paralysis originating in an existing purulent otitis media with acute labyrinthitis may be an indication for a **labyrinthectomy** in order to prevent a threatening meningitis, provided the focus of the facial paralysis can be located in the internal auditory meatus.

The surgical repair of facial nerve paralysis is discussed in a clinical presentation by A. B. Duel and T. G. Tickle (Ann. Otol., Rhin. and Laryng. 45:3 (Mar.) 1936). Six years have elapsed since Sir Charles Ballance and Duel began to work together on the operative treatment of facial palsy. The **Ballance-Duel operation** is the result of continued experimental work on animals. This work brought out also the employment of the degenerated anterior femoral cutaneous nerve for repair material. The authors believe that this hastens the time and probably improves the quality of the direct line repair of the facial nerve. It is now superior to the anastomosis of any of the adjacent motor nerves in the neck for the repair of facial nerve palsy.

It is emphasized that surgery of the facial nerve can only be learned by cadaver experience. Tickle and Duel have seen well over 100 cases of facial palsy, of which 87 were selected for operation, 77 by Duel and 10 by Tickle. The operative technic has been developed by frequent returns to the morgue to work out an idea which was verified or abandoned by trial on the cadaver. Seventeen cases were shown to demonstrate results in a cross-section of the most varying types of cases, ranging

from the early cases, where the undegenerated graft was employed, up to the present, where only degenerated grafts were used. No case of repair of the facial nerve can ever be perfect. Although there may be emotional as well as voluntary control, and although movements may be synchronous with the other side, the best repair that will ever be made will never equal the normal side. Education of the defective side by voluntary control through the neokinetic nervous system may improve facial expression tremendously. The reason for this imperfection in the repaired side is due not so much to a lack of restoration of as much vigor to the recovered muscle, as it is to the fact that split neurons, wandering to the wrong destination, produce on stimulation an asymmetry of response in the facial muscles.

Attention is called to a somewhat more clarified attitude toward cases of so-called "Bell's palsy," and 3 cases are cited to illustrate the authors' position in regard to an **early decompression** which in their opinion insures as nearly a perfect recovery as is obtained in the acute cases of injury.

In the *after-care* of surgical repair of the facial nerve, Duel and Tickle (*Ibid.*) state that the successful recovery in operations performed for facial palsy due either to accidental injury or a so-called "Bell's palsy," or from toxic invasion, depends not only on the technic of the operation but also quite as much on the after-treatment. The external auditory canal must be thoroughly sterilized. It is filled with a 3 per cent. **tincture of iodine**, allowed to remain for 5 minutes and withdrawn, then replaced by 1 or 2 instillations of 95 per cent. **alcohol** within the next few minutes. The canal is finally washed out thoroughly with **normal saline solution**. Since using this technic, there has

been no suppuration following operation in the clean cases.

The 2 types of cases for operation are: First, those due to accidental injury of the facial nerve in operations on the mastoid; and second, those in which toxic infection or refrigeration of the facial nerve have produced a facial palsy. Such cases may be of long standing with a partial recovery of facial movements, or of comparatively short standing with a complete palsy. If an injury of the facial nerve has caused the paralysis of the facial muscles, an immediate investigation has the advantage that the segment of the facial nerve distal to the injury retains response to faradic stimulation for from 48 to 72 hours. In those cases in which the faradic response has been absent for days, months or years, the anatomic dissection of the nerve over the point of injury must be done without the aid of faradic response in the distal segment.

It has been concluded that in all cases it is better to expose the nerve from the stylomastoid foramen up to and proximally beyond the injury. Even in the cases which are to be decompressed, only the outer half of the bony tube distal to the injury should be removed, all the way from the stylomastoid foramen up. The main points in the dressing technic are described.

The final closure of the wound must depend on judgment in each individual case. Where the wound is sufficiently filled in with healthy granulations, **plastic closure** may be done at any time. With degenerated grafts, it has been found of some advantage to postpone the plastic closure for at least a month.

As regards the subsequent treatment of operative cases by electric stimulation, it is believed that faradic stimulation is useless except for purposes of diag-

nosis, and, therefore, this stimulation is not employed in recovering cases or in cases of partial paralysis. **Galvanic electricity**, the interrupted anodal closure over the muscles of the face, for a few minutes once or twice weekly before and after **ionization**, is beneficial in keeping up the tone of the muscle. Operation is not advised in cases where there is no response in the muscle to galvanic stimulation. Galvanic stimulation is continued until facial movements have reached their maximum improvement.

**Gradenigo Symptom Complex.**—

The development of a paresis or complete paralysis of the external rectus muscle of the eye during the course of a purulent infection of the middle ear, with or without a mastoid involvement, is indicative of some pathological process in the petrous bone causing a secondary neuritis in the sixth or abducens nerve, according to M. J. Ballin (M. Rec. 143:411 (May 20) 1936). This disturbance in the nerve becomes manifest in an impaired mobility of the eye, causing a partial or complete paralysis of the external rectus muscle. As a result of this lost muscular action, the eye can no longer be rotated externally beyond the median line. This phenomenon, known as the Gradenigo symptom complex or syndrome, was first described by Gradenigo of Turin, Italy, who in 1904 called attention to this otitic complication. Cases are grouped into 3 distinct classes. According to Gradenigo, the changes in the nerve are brought about by a circumscribed serous leptomeningitis which has become localized near or around the tip of the pyramid. The anatomic relations of the sixth nerve are reviewed, emphasizing that it is in close proximity to the aural structures. There are 4 paths by which the infection extends inward, causing an involvement of the abducens nerve. The Gradenigo

complex presents itself in various forms and in varying degrees of intensity so that it can be classified into 3 distinct groups. Definite symptoms manifest themselves. The treatment must be directed to eliminating the primary focus of infection and this can be accomplished only by thorough **operative measures**. The *prognosis* is favorable in the majority of cases, particularly if the process around the tip is of nonpurulent nature.

Summarizing, Ballin states that:

1. The Gradenigo symptom complex is an unusual rare otitic complication.

2. Although cases have been reported of spontaneous cure, the most certain results are obtained by early and prompt surgical intervention on the mastoid process and middle ear in order to eliminate the original focus.

3. When these foci have been removed, the edema at the petrous tip gradually resolves, the sixth nerve becomes active again, and the external rectus muscle assumes its normal function.

**Petrositis.**—While there may be some differences of opinion concerning the typical *symptoms* of petrositis, certain symptoms are usually prominently present. According to S. J. Kopetzky (Arch. Otolaryng. 22:513 (Oct.) 1935), the following symptoms, signs and findings may be regarded as typical of suppuration of the petrous apex: 1. Neuralgiform pain, especially over the area supplied by the ophthalmic branch of the trigeminal nerve; 2. a discharge from the ear or mastoid wound, (a) recurrent or (b) continuous; 3. a low-grade sepsis; 4. frequently paralysis of the sixth cranial nerve; and 5. x-ray observation showing destructive changes in the petrous tip.

The clinical picture, unfortunately, frequently runs an atypical course, and death may ensue without the previous appearance of suspicious symptoms. The

onset of the clinical signs of suppurative apicitis usually occurs following a simple mastoid operation, performed to drain acute suppurative mastoiditis. Rarely, the symptoms appear in acute suppuration of the middle ear, which may or may not be complicated by suppuration of the mastoid. Pain deep in the eye or around the eye is characteristic when present. The pain is agonizing and nocturnal. There are periods of complete absence of pain. Other symptoms, such as palsy of the sixth nerve, labyrinthine and meningeal irritation, are sometimes noted but cannot be considered as a definite part of the picture.

### CAVERNOUS SINUS THROMBOSIS.—*Pathogenesis.*—

The pathogenesis of cavernous sinus thrombosis is discussed by L. A. Scarpellino, P. F. Stookey and F. J. Hall (J. Missouri M. A. 33:251 (July) 1936). The authors do not deny that cavernous sinus thrombosis which occurs following infections in the so-called danger area cannot be produced by organisms other than the *Staphylococcus*. They believe that it is impossible for any organism producing a soluble exotoxin or containing an endotoxin to produce cavernous sinus thrombosis. However, in 7 cases under their observation, 6 of which came to autopsy and bacteriologic studies done, the *Staphylococcus* was isolated in all instances. The filtrate produced from these cases, in which a positive culture was obtained either from the blood or spinal fluid, showed the property of hemolyzing red blood cells, of producing necrosis when injected into the back of an experimental animal, and forming thrombi when injected in the marginal veins of the ear of a rabbit. From the experience of the authors, it is their opinion that the *Staphylococcus* toxin has the property to enhance the coagulability of the blood and produce marked

changes in the intima of the veins, associated with edema and changes in the surrounding tissue. With such extensive vascular pathology produced by the filtrate or toxin alone, this filtrate must be looked upon as a toxin elaborated by the metabolism of the bacteria. Therefore, the thrombosis of the vessels would be enhanced by the presence of the organisms and production of their toxin *in vivo*.

That the staphylotoxin is made up of many factors is still to be adjudicated. By many workers it is thought to contain at least 5 components; *viz.*, a hemolysin, a leukocidin, a necrotoxin, a plasma coagulating substance, and a lethal factor. However, all these factors of the staphylotoxin are neutralized by the same antitoxin. From the fact that the *Staphylococcus* toxin is bound by *Staphylococcus* antitoxin *in vitro*, the question immediately arises as to the therapeutic use of antitoxin in the attempted treatment of cavernous sinus thrombosis. When the clinician has the opportunity to observe, at postmortem, the cavernous sinus filled with a septic thrombus and the contiguous portion of the sphenoid bone and the hypophysis to be partially liquefied by the lytic influence of the toxin, together with the coexisting evidence of a widespread septicemia with innumerable abscesses in the lungs, septic infarcts in the kidneys, and frequently thrombi in the larger vessels throughout the body, he is overwhelmed with the hopelessness of any therapeutic procedure. It may develop that the therapeutic possibilities of antitoxin are prophylactic. The authors had an opportunity to treat a case of cavernous sinus thrombosis of staphylococcic etiology with **Staphylococcus antitoxin**. After the administration of large amounts of commercial *Staphylococcus* antitoxin, the immune liter was enhanced to twice that of the normal. The original read-

ing showed no natural antitoxin. This indicates to the authors that there may be a period in *Staphylococcus* septicemias in which free toxin circulates in the blood and fixes itself irreversibly to tissue cells, particularly the heart, liver and kidneys, and causes irreparable damage that no amount of added antitoxin can influence. It is obvious that the administration of antitoxin can only neutralize the circulating toxin not bound to tissue cells.

The authors state in conclusion that no definite facts can be deduced from such a small series of cases, but experiments suggest that the toxin filtrates elaborated by the growth of the *Staphylococci* area are a potent factor in the production of cavernous sinus thrombosis. In their experience, cavernous sinus thrombosis, of the anterior type, is almost invariably associated with a staphylococcal infection, although cultures may reveal other bacteria present.

**MÉNIÈRE'S DISEASE.**—The precise definition of Ménière's symptom complex is still unsettled. (Editorial: Eye, Ear, Nose and Throat Monthly 15:307 (Oct.) 1936). In fact, this lack of agreement on the part of otologists has in no small way contributed to the confusion which results in every case of persistent aural vertigo. The non-uniformity in diagnostic findings and the ever-changing interpretation of these findings have led some writers to make deductions which are not altogether scientifically sound. A. Thornval believes that Ménière attacks are brought on by a sudden, often almost explosively developing hyperfunction of the vestibular system on one side. According to Just, Ménière's symptom complex is nothing more than an angioneurosis, especially of the acoustic nerve. He contends that Ménière's disease is usually seen with unilateral or bilateral infection

in the upper air passages and that the symptoms promptly disappear when the nasal condition is cured.

E. Foldes (Am. J. Digest. Dis. and Nutrition 2:243 (June) 1935), in discussing a new concept of the disease with its response to antiretentional therapy, states that there seems to be a striking similarity in the pathogenesis of Ménière's disease to epilepsy, eclampsia or pregnancy, eclampsia of infancy, migraine, angina pectoris, bronchial asthma, the allergic diseases and gout. These diseases manifest themselves in the form of attacks which appear to be due to a retention of water and minerals that is local and temporary, rather than generalized and continuous. The attacks cease when the retained liquids disappear from the respective organ.

For the *treatment* of this group of diseases, an antiretentional therapy has been developed which employs a **diet** based on the recognition of the fact that all food elements, such as proteins, carbohydrates, fats, water, minerals and vitamins influence the water and mineral metabolism. The author found that, while the antiretentional diet in itself, or together with the administration of phenobarbital, is ineffective, the addition of **quinine sulphate**, **phenobarbital**, and the **extract of nux vomica** to this diet, the protein content of which is slightly lowered, is followed by a complete disappearance of the attacks within a few days, with no relapses observed thus far. A complete abolition of the attacks, such as Foldes observed in his 4 cases, can hardly be ascribed to the medication in itself. The results observed, he believes, are not attributable to the administration of quinine sulphate by itself, but to the concerted action of quinine sulphate and the diet.

W. E. Dandy analyzed the signs, symptoms and treatment of 42 cases of Ménière's disease and found it to be

twice as frequent in males as in females, and more often on the left than on the right. So far as the dizziness is concerned, its character was most variable, always with a sensation of objects moving in a rotation fashion. The vertigo together with the other characteristic symptoms which are cited in Dandy's analysis render a diagnosis not particularly difficult, but with the triad of deafness, dizziness and tinnitus, other findings are only of incidental diagnostic value.

*Treatment* has presented a difficult problem. The more conservative otologists are inclined to the medical side, the less conservative to the surgical. Certain drugs like **luminal** have been found by some workers to be palliative, especially during a severe attack. Dandy treats the disease by **sectioning the auditory nerve on the side** known to be affected. It is therefore important to differentiate between the true and the pseudo-Ménière's disease.

S. N. Parkinson reports a case of so-called Ménière's syndrome and suggests the descriptive term recurrent aural crisis (Ann. Otol., Rhin. and Laryng. 44:382 (June) 1935). **Endolymph decompression**, as described by Portmann, was performed on the involved side. The effect was promptly and favorable to modify the course of symptoms sufficiently to rehabilitate the patient. Continued deterioration in auditory and vestibular function indicates that the disease process has not been terminated in spite of symptomatic relief. The relation of endolymph decompression to the symptomatic course of this disease may be significant in studies aimed at etiology and pathology. It seems consistent with Furstenburg's work on salt retention. It suggests that the endolymph is concerned in the pathology and in the production of the characteristic attacks.

Since August 1931, K. G. McKenzie (Canad. M. A. J. 34: 369 (Apr.) 1936) has carried out **unilateral section of the vestibular portion of the auditory nerve** on 12 patients. As a result of this experience, he has concluded that it is possible to section the vestibular portion of the nerve with sufficient accuracy for clinical requirements. The caloric response is abolished and the attacks of vertigo cease, while at the same time the cochlear fibers function as before operation. The first patient was operated on in August, 1931, but proved to be an unsatisfactory subject, as she had little or no hearing before operation. The second patient, however, had good hearing and satisfactorily proved the possibilities of this new procedure. One of the 12 patients died from a wound infection 11 days after operation. Apart from this unfortunate mishap, the results obtained have been very satisfactory. They are all extremely grateful for the relief which they have obtained, and although the postoperative period is short, varying from 3 years and 5 months to 5 months, there has been no reason to anticipate a return of attacks. For a few weeks or months there has been a moderate degree of unsteadiness. This gradually disappears and patients become confident and cheerful and quite certain of their balance. Occasionally, on turning quickly in the dark, there is a slight tendency to fall to the involved side. Of 9 patients, 2 have had complete cessation of tinnitus, 2 were unchanged, and in 5 there has been a marked diminution. With 2 exceptions, all patients had an absence of the caloric response after operation. These have remained free from attacks, and this observation suggests that it is not necessary to cut all vestibular fibers to cure a patient. Of the 12 patients, 7 had such poor hearing on the involved side that it was of little importance to

save the cochlear fibers. In each instance, however, the hearing which they did have was not impaired by the operation and they have remained free of attacks. The remaining 5 patients had useful hearing, but 2 failures occurred in this group. One patient died and in the second case the cochlear fibers were unintentionally cut. The records of hearing before and after operation on the other 3 patients with good hearing illustrate the value of this operative procedure when it is desirable to save the cochlear fibers. The records show that hearing is being maintained on the involved side.

**DEAFNESS.** — A preliminary presentation of the scholastic and personality changes attendant on the irremediably hard of hearing child is presented by A. J. Hofsommer (J. A. M. A. 107: 648 (Aug. 29) 1936). Specific cases are cited bearing out the belief that the low intelligence quotient of the deafened child is often due to lack of hearing experience and not to deficient mentality. Statistically, there are among hard of hearing children 3 times as many repeaters as among their normal companions. Tables are furnished which show a comparison of a hard of hearing group of children who were instructed in lip reading, with a hard of hearing group who refused lip reading, owing to lack of parenteral coöperation or to unwarranted prejudice or advice.

The conclusions arrived at by the author are:

"1. The education of the unassisted hard of hearing child is an interrupted learning, an imperfect acquisition of knowledge.

"2. The hard of hearing child should not be segregated from the public school class room, but lip reading should be a part of the curriculum.



"3. The hard of hearing child in a majority of cases has a low intelligence quotient because of lack of educational experience and not because of deficient mentality.

"4. Lip reading was given in the public schools of Webster Groves, St. Louis County, to a group of hard of hearing children. After from 1 to 3 years, 47 per cent. showed an increase in their intelligence quotient, 41.1 per cent. showed no change, and 11.7 per cent.

showed a drop in intelligence quotient. In 76.4 per cent. definite class room improvement was made. All showed marked betterment in behaviorism.

"5. In contrast, another group of hard of hearing children who refused lip reading showed no increase in their intelligence quotient during the same period, but 75 per cent. showed a drop; only 18.7 per cent. made classroom improvement, and all were character problems.

## LARYNGOLOGY

By LOUIS Z. FISHMAN, M.S., M.D.

### **PATHOLOGIC PHYSIOLOGY.**

—*Laryngeal spasms* (adductor type) have been observed not uncommonly following laryngeal and extralaryngeal manipulations. Certain fatal surgical accidents, which are not attributable to the immediate procedure, have most usually been labeled thymic deaths. Yet a considerable literature, scientifically constructed, is available which questions the validity of any such interpretation. Further, clinicians know what varied remote effects may result reflexly. Despite this basic knowledge, a sudden death—or spasm of one or more muscular groups, when occurring as an incidental event to remote manipulations—often remains mysterious and unexplicable. The following experimental studies of "reflex closure of the glottis by stimulation of afferent (visceral) nerves" by U. Brewer, A. B. Luckhardt, W. M. Lees and D. S. Bryant, add more links to the chain of evidence which may lead to a better understanding of such pathologico-physiologic phenomena.

At this time (1934), it was graphically demonstrated that traction, performed on any of the splanchnic viscera, produced cessation of respiration with an approximation of the vocal cords.

When an inspiratory phase broke through, the abduction was relatively feeble, indicating the presence of an increased adductor tone. The tone was maintained for some time after traction had ceased, gradually subsiding. Electrical stimulation of the splanchnic nerve led to the same glottis responses as those which were seen with visceral traction, but the adductor spasm was more marked. A further check on graphic records was made by obtaining action potentials from one of the recurrent nerves while visceral traction or splanchnic stimulation was performed. The conclusion drawn was that traction on the splanchnic mesentery or direct stimulation of splanchnic (afferent) nerves, by causing a partial or complete closure of the glottis (adductor spasm), may be factors in the production of the asphyxial conditions which may occur during certain steps in some abdominal operations. That the splanchnics are the only afferent pathways from the viscera of the abdomen was demonstrated by N. Brewer and D. S. Bryant (*Anesthesia and Analg.* 14:190 (July-Aug.) 1935). They showed that blood-pressure, sympathetic and spinal cord pathways have no part in the reflex arc.

**PARESIS AND PARALYSIS.—**

L. Z. Fishman (Arch. Otolaryng. 24: 118 (July) 1936) offers evidence, both clinical and experimental, which indicates that no simple explanation may be given to account for the various positions assumed by paretic or paralytic vocal cords. He describes the Rosebach Semon "law" as a hypothesis too simple to account for the complex neurophysiologic mechanisms involved in normal and abnormal activities of the laryngeal musculature. A case of temporary glottic spasm occurred in a boy, aged 14, during prolonged suspension laryngoscopy for purposes of obtaining a motion picture record of this boy's larynx. There was a preëxistent cardio-spasm. The following outline of plausible etiologic factors is given:

1. Physiologic fatigue of the abductors.

2. Autonomic nervous system in fatigue of the striated muscle.

3. Abductor psychasthenia or abductor neurosis.

4. Injury to the vagus (tenth) and to the eleventh cranial nerve or to its laryngeal branches.

5. Hyperphonasthesia or persistent reflex stimulation by instrumentation. The term "phonasthesia" is suggested as descriptive of the visceral proprioceptive sense (the latter, a term advanced by Otto F. Kampmeier), which is most probably recorded subconsciously in all during phonation. "Hyperphonasthesia," then, refers to an exaggeration of these afferent impulses. It is hypothecated that when the bulbar, thalamic and cortical centers for the larynx are subjected to an exaggeration of visceral proprioceptive impulses, glottic spasm follows.

6. Persistent stimulation by the local action of abnormally large amounts of inspired air, reflexly initiating glottic closure.

7. Persistent hyperpneic stimulation—the laryngeal test *besoin de respirer*.

A second case of postthyroidectomy bilateral "abductor" paralysis was studied by L. Z. Fishman (*loc. cit.*) with the idea of determining the extent of neuromuscular destruction and its association with psychoneurotic dispositions. By injecting 2 per cent. solutions of procaine hydrochloride directly into the cricothyroid and interarytenoid muscles particularly, the status of the larynx was found to be that of a complete recurrent nerve destruction. Further, attacks of dyspnea were determined to be due, not to subglottic inflammation and edema, but rather to a spasticity of the tensor and sphincter muscles (interarytenoid, aryepiglottic, etc.), so that the supraglottis was completely shut by a muscular ring in the manner of a membranous sphincter. This sphincteric action was alleviated by hypnotic treatments administered by a psychiatrist (S. H. Kraines).

The following conclusions by Fishman are of interest:

1. The case presented is either one of laryngismus stridulus (hyperphonasthesia) or of abductor psychasthenia, and a diagnosis of flaccid abductor paralysis is as correct clinically and experimentally as the generally accepted one of spastic adductor paralysis.

2. There is no apparent proclivity of organic abductor paralyzes or of functional adductor pareses; abductor psychasthenia predicates the not uncommon occurrence of functional abductor paralysis or, rather, abductor paresis.

Nor is there any difference in the vulnerabilities between abductor or adductor neurons or peripheral nerve fibers; differences depend, instead, on whether a lesion is irritative or degenerative. When unmyelinated, adductor nerve fibers are demonstrated to be in-

volved, the laryngologist will have a cause for using the term "vulnerability."

3. A diagnosis of a lesion of a peripheral nerve as irritative or degenerative may point to a rational form of therapy and avert many contemplated surgical procedures on the larynx, procedures which are too frequently futile. Any procedure that is employed to correct motor dysfunctions of the larynx should be aimed first at a physiologic restoration of function. Cordopexy, which offers mechanical restoration of laryngeal patency, should be performed only as a last resort.

4. The term "phonasthesia" is suggested as descriptive of the intrinsic sensibility of the larynx. Hyperphonasthesia is a definite, though for the present it is more or less a metaphysical, state of the larynx, which may easily simulate spastic adductor or flaccid abductor pareses.

5. Whether or not *besoin de respirer* or a modification of it is a valuable neurologic test under circumstances which permit direct exposure of nerves, such as might obtain during thyroidec-tomies, and whether or not the test is of sufficient value in other cases to warrant surgical approach to the nerves of the larynx for a diagnosis, depend on future reports of work continued along principles more or less similar to those outlined. Also, the thought is not amiss that some laryngologists might employ this test as the first step in performing a cordopexy. Should abduction of vocal cords which were previously fixed in the midline be obtained, the diagnosis of spastic paresis of adductors rather than of flaccid paralysis of abductors would be established, the operation interrupted, and more rational methods of treatment entertained.

6. Electrotherapy for laryngeal motor disturbances is of no value in cases of spastic adductor or flaccid abductor

paralysis, because, under the conditions, these muscles would be aided physiologically in their pathologic states. Experiments performed on patients form the basis for the statement that such therapy, as commonly employed, cannot accomplish even these harmful effects. In selected cases of *flaccid paralysis*, direct **peroral faradization** of the involved muscles by use of the induction coil or Sine machine may have beneficial effects. At least, such an attempt is rational.

**PARALYSIS.**—Hoarseness or aphonia in the presence of organic paralysis of the vocal cords does not preclude a hopeless attitude with regard to phonation. E. Fröschels (Arch. Otolaryng. 23:599 (May) 1936) describes a case in which the left labium vocale was fixed in the paramedian position. Complete aphonia occurred in this patient 4 months after an operation for goiter. The treatment applied in cases of paralysis of the soft palate was used, *viz.*, by employing pushing movements of the hands downward, the power of the muscles brought into action was transmitted to the larynx. For this treatment the **hands are placed lightly on the chest and are pushed downward while vowels are uttered.** Intonation should be made too late or too early, but the sounds should not be uttered until the arms are in the downward movement. Under the influence of this treatment the patient's condition improved considerably and after a year she was able to sing. Laryngoscopy revealed that the paramedian position of the left labium vocale was not changed but that the right labium moved freely in both directions.

**NONDIPHHTHERITIC LARYNGOTRACHEITIS.**—An epidemic in Los Angeles during the fall and winter of 1933-1934 of this type of infection in children is reported by W. J. Smith

(*Ibid.* 23:420 (Apr.) 1936). The severity of laryngeal symptoms in children is explained by the existence of distinctive anatomicohistologic characteristics. The subglottis of a child is so small that very little inflammatory change is necessary to cause the loose areolar tissues of this region to swell sufficiently to close off the trachea below. The chief offending organism was found to be the streptococcus, although it was usually found in conjunction with other bacteria. In 4 fatal cases the severity of the symbiotic relationship of *streptococcus hemolyticus* and *staphylococcus aureus* was shown in that their co-existence was found in 3 of these cases. In the 1 other fatal case, *streptococcus hemolyticus* (*beta*) was responsible. A fulminating case of *laryngotracheal bronchitis* is reported by D. Davis (*Ibid.* 23:686 (June) 1936) which occurred in a female, aged 29 years. Death occurred despite tracheotomy and other therapeutic measures, due to associated bilateral bronchopneumonia, toxic myocarditis, toxic splenitis, hepatitis and nephrosis. Pure tissue cultures of *staphylococcus aureus* were obtained. Obstruction to respiration played no part in this case. A differential diagnosis, even in the face of an epidemic, should exclude diphtheria and a foreign body.

Therapeutic measures are directed first against the severe toxemia which is present in many cases. This includes a high intake of fluids and the administration of antipyretics. Hydrotherapy is of value. Secondly, inhalations of tincture of benzoin in a room of constant temperature is valuable in the following manner: All doors and windows of the room should be kept closed, excepting for one open transom leading into the general quarters; a croup tent completely covering the patient and bed except at one side is constructed; the croup kettle is adjusted

so that the vapor spout enters the foot of the bed; hourly observations of two room thermometers are made, and recorded and an even temperature of from 76° to 78° F. (24.4° to 25.5° C.) should be maintained; the temperature in the tent should vary between 80° and 82° F. (26.6° and 27.7° C.). Sedatives should rarely be given, since the dyspnea is obstructive in type and not spastic. **Respiratory vaccines**, according to Forber and Baums' abortive technic, are given when the patient is seen early, in 0.25 c.c. doses of the double concentrated vaccine and repeated from 12 to 24 hours, if necessary, depending on the reaction. The second dose is increased to 0.5 c.c. within 10 hours after the first dose. If a tracheotomy is not necessary by this time, it may be assumed that the patient is out of danger. In the severe forms, delay is dangerous. Surgical intervention is usually called for, which in Smith's series of 43 cases consisted of **tracheotomy**, under local anesthesia, in 12 cases. General anesthesia is contraindicated on account of its bad effect on the accessory muscles of respiration. The following instructions for tracheotomy and admonitions regarding its after-care are classical:

Two factors are essential for a good tracheotomy, *viz.*, 1. someone to hold the head and neck properly, and 2. an assistant who can handle retractors correctly. It is preferable to precede tracheotomy with bronchoscopy, leaving the bronchoscope in place. Tracheotomy can then be done with greater leisure and ease, because the trachea will be easily identified with the tube in it, and at the same time there is no asphyxiation. It is often very difficult to locate the trachea in a fat, short-necked infant of about from 12 to 15 months of age.

As important as the operation is adequate posttracheotomy care: A qualified nurse should be in constant attendance.

A duplicate tracheotomy set and additional equipment should be at the bedside, and suction should be available and used. The inner tube should be removed and cleansed as often as necessary. This may be every 5 minutes, but it must be done and the airway kept clear; otherwise, as Jackson has so often stated, "the child will drown in its own secretion."

The secretion often becomes more viscid and, as a result, forms plugs of mucus that tend to obstruct the bronchi. The placing of a piece of gauze moistened with a weak solution of sodium bicarbonate over the tracheotomy tube will offset this drying effect to some extent. If plugs form, however, bronchoscopic drainage is indicated at once; otherwise, collapse of the affected portion of the lung takes place, the condition progresses, and asphyxiation and exhaustion result.

**TUBERCULOSIS. — Therapy.** — Pain accompanies tuberculous involvement of the larynx in ulcerative processes and various phases of cartilaginous and joint involvement. In addition to the general and local therapy which is directed at a cure of the pathology *per se*, of like importance is the *relief of pain*. Such relief may be vital in maintaining nutrition and is essential if a hopeful mental attitude of the patient towards the disease is to be expected. Therefore, the merit of L. B. Stott's (Brit. J. Tuberc. 30: 109 (July) 1936) correct evaluation of one of the laryngologists most spectacular procedures in his therapeutic armamentarium must be recognized, *viz.*, **blocking of the afferent (sensory) nerves of the larynx**. He points out that the practice of blocking the internal branch of the superior laryngeal nerve, introduced by Hoffman in 1908, still retains its popularity as a method of giving relief in dysphagia. It does not, however, relieve the agonizing pain that shoots from the pharynx to the

ear during the act of swallowing. The normal consummation of the reflex of swallowing is prevented by this type of pain. The obstructed action of the stylohyoid muscle is apparently responsible for the characteristic shooting pain in the ear. Six nerves—the fifth, seventh, ninth, tenth, eleventh and twelfth—all take their part in the act of swallowing, and therefore it is a matter for little surprise that the blocking of one branch of the tenth fails to relieve pain during swallowing, though it does anesthetize satisfactorily the laryngeal mucosa. The mylohyoid nerve, however, is accessible at its point of division from the inferior dental nerve, as it enters the mandibular foramen behind the projection of the lingula. The terminal branch of the facial nerve to the inferior edge of the posterior belly of the digastric muscle is also of easy access, as the anatomic relations of the digastric muscles and its attachments to the hyoid bone have definite surface markings. Thus, it is possible to block the branches of 3 cranial nerves to the parts concerned, leaving the ninth, eleventh and twelfth unaffected. That is to say, by infiltrating the neighborhood of the posterior belly of the digastric muscle with a local anesthetic and at the same time blocking the mylohyoid nerve and the internal branch of the superior laryngeal nerve on both sides, it is possible to render the act of deglutition painless without interfering with mastication or the movement of swallowing, even though occasional unavoidable blocking of the inferior dental nerve produces anesthesia of the lower lip.

**Tracheotomy.**—When tracheotomy is required in cases of pulmonary tuberculosis because of stenosing lesions of the larynx, tuberculous or otherwise, the clinical outcome is not necessarily made worse. M. C. Myerson (Arch. Otolaryng. 23: 1 (Jan.) 1936) confirms

these statements by reporting a series of 9 cases of combined severe primary pulmonary tuberculosis and secondary extrapulmonary lesions, including the larynx to the extent that tracheotomy had to be performed to prevent asphyxiation. Of these 9, far advanced cases of tuberculosis, 3 improved or recovered. He feels that although laryngeal involvement diminishes the prospect of recovery, it does not mean that the tuberculous patient is doomed. The *prognosis* is usually better in those cases in which the pulmonary lesions show a tendency to recover, and in which the sputum contains no tubercle bacilli. Further, when the tracheal wound comes in contact with a large amount of bacillus-laden sputum, it usually becomes infected. Early and energetic attention to the involved larynx accomplished much for these sufferers.

*Physiotherapy.*—Any new method of promise in the relief of the excruciating and debilitating *pain* which occurs in certain types of *tuberculous laryngitis* deserves fair trial by those who understand the problems of tuberculous infections. R. Grain (Tubercle 17:261 (Mar.) 1936) believes that **electrical anesthesia** has advantages over other therapeutic methods in the treatment of painful dysphagia in that it is simple in application, painless, harmless, never producing any local or general reaction, and giving positive results in from 98 to 99 per cent. of cases of dysphagia. Electrical anesthesia, as used in the treatment of painful dysphagia, is a medical anesthesia that consists in eliminating in a localized territory the pain due to evolutive or avoluted lesions. These regional pains form the extensive class of peripheral algias. The electrical anesthesia has no appreciable and durable effect on truncular algias. It must be considered the treatment of only the algias of the nerve endings, on which

it acts with remarkable efficiency. The anesthesia is obtained by **iodide ionization of the larynx** encircled with special electrodes. The ionization current is produced by a galvanic apparatus with a fine reducing coil working on 45-volt dry batteries or on accumulators capable of giving at least 15 ma. As the current must be rigorously continuous, these sources are the only ones that can be used. The electrodes are made of unoxidizable steel with a thickness of 0.5 mm. The anterior electrode is 75 mm. long and 35 mm. wide and the posterior electrode 100 mm. long and 35 mm. wide. The anterior electrode is placed in front of the larynx and the posterior electrode on the nape of the neck. They are kept in position by a collar made of isolating thick rubber. The intensity of the current to be used is uniformly of from 10 to 12 ma.; the sittings last one-half hour, or longer if necessary. The sittings are repeated daily until the duration of the anesthesia reaches 24 hours, after which they are repeated only when the pain reappears. There is no advantage in giving daily sittings once the anesthesia lasts 48 hours, as its progression is not influenced by the repetition. As soon as the current passes, the patient notices a sensation of stricture in the neck, and at the same time he has a taste comparable to that of ink or of copper. The sensation is accompanied by a slight amount of ptyalism. The sensation of stricture disappears in 4 or 5 minutes, while the metallic taste and the salivation persist during the treatment. Five or 6 minutes after the passage of the maximal current, the patient notices a marked diminution of the pain on swallowing, which is reduced to a sensation of slightly disagreeable prickling, and, at the same time, the auricular irradiations disappear. After this beginning, the anesthesia increases rapidly and in about 10 or 15

minutes after the onset of the treatment it is absolute.

**CARCINOMA.—Epiglottis.**—Treatment and prognosis depend upon the site of involvement. For although malignancies at this level are considered as being extrinsic—poor prognosis—differences in response to therapy will be found to occur depending upon the particular region of the epiglottis affected. G. Tucker (Ann. Otol., Rhin. and Laryng. 44:933 (Dec.) 1935) reports a case of a male, aged 67, whose epiglottis was found to be invaded by a mass shown by biopsy to be squamous cell carcinoma, Type No. 1. Since the outer laryngeal surface was invaded and there being no demonstrable cervical lymphadenopathy, **extirpation of the epiglottis** alone was decided upon as the more conservative procedure in preference to laryngectomy. The rationale of such a procedure was based upon the barrier effect of the elastic fibrous cartilage of the epiglottis to the extrinsic structures of the larynx.

*Technic.*—A preliminary tracheotomy was performed 10 days prior to the extirpation by the thyrotomy route. The anterior ends of the ventricular bands were included in the extirpation by subperichondrial resections of the notch and portions of the laminae of the thyroid cartilage. Also, a goodly portion of both aryepiglottic folds were removed. Hemostasis was easily obtained by clamping and ligating visible points of bleeding. The mucous membrane which covered the valleculæ, or lingual surface of the epiglottis, was used as a flap to cover the denuded area. The thyrohyoid membrane and the tissues on either side were pulled together with a deep silk worm gut suture, which was carried around from the thin surface on one side, including the tissues where the base of the epiglottis had been attached and coming from within outward through the skin on the opposite side. This deep suture closed completely the opening remaining after the removal of the epiglottis. Indirect laryngoscopy revealed the cords to be approximated perfectly with good function.

The convalescence was undisturbed. The only difficulty was encountered when an attempt to remove the nasal feeding tube was made after the fifth day. Dysphagia and aspiration was gradually overcome, permitting the removal of the feeding tube at the end of the seventh day. The patient was discharged at the end of 2 weeks, the tracheotomy tube having been removed and difficulty in swallowing having been practically overcome. At the end of 3½ years the patient's larynx is in excellent condition.

Much remains to be written about cancer, whether it be of the larynx or of any other histologically-analogous organ. It will suffice this year to cover the subject with the review of an exhaustive statistical report by S. W. Garfin, of the Cancer Commission of Harvard University (New England J. Med. 213:1109 (Dec. 5) 1935). These 202 cases are unselected, consecutive ones of cancer of the larynx treated at the Collis P. Huntington Memorial Hospital over a period of 14 years, dating from January, 1919 to July, 1933. During this period there were 12,466 cancer patients admitted, giving an incidence of 1.6 per cent. for cancer of the larynx. Many were far advanced (extrinsic) types, commonly the result of the hopeless attitude assumed among some in the profession, and the failure to recognize the early symptoms of laryngeal cancer. Early diagnosis offers a patient his best chance of cure. This is shown to be especially true of the early intrinsic type by the following statistics.

Coutard's method of **x-ray therapy** in 77 cases is considered summarily as follows:

1. Cure of cancer by x-rays is still difficult.
2. Cure of cancer by x-rays is still dangerous.

3. A very small margin exists between the dose which will determine a cure and the dose which will provoke an injury.

4. The daily examination of the patients is necessary; modification of normal tissues and of the general condition by x-ray treatment sometimes appears so quickly that it is often necessary to diminish the daily dose or the size of the fields in the course of treatment.

**Etiology.**—Although this is unknown, predisposing causes are overuse of the voice, heredity, irritant inhalations, excessive use of tobacco and alcohol. Tobacco plays a questionable irritative rôle. Repeated injury, long-continued irritation, and inflammation are potential factors of cancer. Leukoplakia is recognized as a definite precancerous lesion. Garfin (*Ibid.*) states that he possesses a pathological slide showing the transition from leukoplakia to carcinoma. Malignant transfusions of a benign, papillomatous growth into a malignant process is explained by Ewing in 4 possible ways:

1. The original disease is a simple papilloma which really changes its clinical character and develops infiltrative growth.

2. The original disease is carcinoma, but the examination is from tissues which are inadequate as specimens.

3. An original papilloma is removed, but the disease occurs elsewhere as a carcinoma.

4. An original papilloma is imperfectly removed and the remnant is stimulated to a typical cancerous growth.

**Age.**—This is an important factor as shown by the table.

**Signs and Symptoms.**—**Duration.**—It is surprising to see patients in advanced stages of involvement by cancer, which has been asymptomatic until as short a time as 6 months prior to their

| AGES AND SEX                   |              |                |
|--------------------------------|--------------|----------------|
| <i>Age of Onset by Decades</i> |              |                |
| <i>Ages—Years</i>              | <i>Males</i> | <i>Females</i> |
| 20 to 30.....                  | 0            | 1              |
| 31 to 40.....                  | 9            | 0              |
| 41 to 50.....                  | 34           | 4              |
| 51 to 60.....                  | 72           | 3              |
| 61 to 70.....                  | 47           | 8              |
| 71 to 80.....                  | 15           | 4              |
| 81 to 90.....                  | 2            | 0              |
| Age not stated. . . . .        | 3            | 0              |
|                                | 182          | 20             |

first symptom. The shortest duration found by Garfin was that of a man aged 65, who complained of a sore throat for 1 month before admission. The longest duration was in a man 57 years of age who was hoarse for 10 years.

**Symptoms** will vary with the site of the lesion and will depend largely upon how much the normal function of the larynx is impaired. A growth situated on the edge of the cord near the anterior commissure will cause more hoarseness, because it prevents complete closure of the glottis, than a larger growth on the cord in the region of the posterior commissure where the closure of the glottis is not so much affected. In early stages, there may be, however, either no symptoms or merely fatigue of the voice or transitory hoarseness. As the growth progresses and invades the glottis, the hoarseness becomes more pronounced. This may go on for months, or even years, as observed in some cases. The patient, or perhaps his medical attendant, regards it as "cold." With the advance of time, the voice becomes altered, and the breathing is impaired, especially on exertion. The voice may be reduced to a coarse whisper, finally leading to aphonia.

The mild symptoms very often complained of by the patient bear a disproportionate relationship to the size of the lesion and the seriousness of the



condition. Generally speaking, however, the intrinsic type is characterized by a varying degree of hoarseness in the early stages. As time progresses, the hoarseness is increased and normal respiration is interfered with, often leading to aphonia and dyspnea. Pain is not usually a factor in this type of lesion. In the extrinsic types, again, the symptoms vary greatly with the site of the lesion and its extent. There is at first some vague discomfort in the throat, such as a feeling of a lump or perhaps some slight difficulty in swallowing. As time goes on, these symptoms increase in severity. Pain is at times quite common in this type and is very often referred to the ear.

*Enlargement of Cervical Glands.*—In 22 patients, the sole complaint was a swollen neck and no other discomfort.

*Site of Lesions.*—The intrinsic types occurred in 81 cases; 63 of these were on the cords. [Certain clinics consider any other site of involvement as extrinsic in character.—REVIEWER.]

*Diagnosis.*—It is not always possible to make an early diagnosis and the following are some of the reasons for this:

1. The remote location of the tumor.
2. The symptoms may be slight, especially in the early stages of the intrinsic type.
3. Rapidity of the growth, which may be very marked in some instances.
4. Early necrosis and metastases, especially in the extrinsic variety.
5. Early and rapid invasion of surrounding cartilages. The early diagnosis of cancer of the larynx, especially in the intrinsic type, is of the greatest importance. Contrary to the opinion held by many physicians, the prognosis in this type is good when diagnosed early and treated promptly. *Biopsy* is of utmost value in establishing a diagnosis. Garfin states that a biopsy is performed in every case except in those patients in

whom the disease has progressed to such an extent that the physical condition contraindicates even this minor procedure.

*Differential Diagnosis.*—In the differential diagnosis of laryngeal cancer, consideration must be given to chronic laryngitis, syphilis, tuberculosis, pachydermia, perichondritis, angiomas, laryngeal polypi and benign growths. Of course in the advanced cases, diagnosis is not so difficult, but even here, the other two members of the triad, syphilis and tuberculosis, must constantly be kept in mind.

*Tuberculosis.*—The tubercle shows a predilection for the posterior part of the larynx, especially the posterior interarytenoid commissure and, depending upon the stage of the disease, there may be either infiltration, proliferation or ulceration. Primarily, tuberculosis is an ulcerative process and does not have the same tendency to proliferate as cancer. It is more probable to mistake tuberculosis for cancer than *vice versa*. Also, it is always secondary to pulmonary tuberculosis. An examination of the chest will help to rule this out. It must always be borne in mind that tuberculosis and carcinoma may coexist in the same larynx.

*Syphilis.*—Syphilis is usually more widely disseminated in the larynx. The larynx is markedly congested. The diagnosis is greatly aided by the history of infection and serological examination. When ulcerations are to be seen, they are usually punched-out and deep, sometimes in gummatous infiltrations.

*Fixation.*—Does not necessarily occur in early cases of intrinsic cancer of the larynx. When it does occur, it denotes a considerable progression of the lesion. A slight limitation of movement is highly significant. If the slightest doubt occurs, biopsy should be performed.

**Pathology.**—Most of Garfin's cases were of the squamous or epidermoid variety of carcinoma. Four were papillary carcinoma; in 11 patients there is histopathological and clinical evidence that the disease began as a benign papilloma and subsequently transformation to carcinoma occurred. The transition period was very variable, 3 months in one case and 10 years in another.

**Grades.**—Broders' grading of potential malignancy, modified by Gates and Warren, has been employed in the Collis P. Huntington Memorial Hospital since 1928, and since then 38 cases have been so classified. There were as follows: Grade I, 13; Grade II, 19; and Grade III, 16 (Garfin, *loc. cit.*).

**Treatment.**—Intrinsic cancer of the larynx, although insidious in its onset, has the favorable characteristic of remaining localized for a long time before spreading to the neighboring lymphatics. Just how long it may remain localized, it cannot be said with any degree of certainty, but in some probably as long as 2 or 3 years. Furthermore, the greater number of these tumors are of low grade, Grades I and II. Therefore, if the patient can be seen early, and if he will consent to have an adequate operation performed, his chances of a permanent cure are very good. In this series, unfortunately, there were only 19 cases considered at all favorable for operation and 2 submitted to operation.

The treatment carried out in this series was as follows:

|  |    |
|--|----|
| Total laryngectomy .....               | 7  |
| Laryngofissures or hemilaryngectomy.   | 12 |
| Partial operation with radium .....    | 20 |
| Radium alone .....                     | 33 |
| X-ray alone .....                      | 37 |
| Radium with x-ray .....                | 40 |
| Resection of glands with irradiation.. | 6  |
| Resection of glands only .....         | 2  |
| Partial operation .....                | 2  |
| Tracheotomy alone .....                | 17 |

|  |    |
|--|----|
| No treatment .....                     | 19 |
| Seeds to glands.....                   | 1  |
| Branchial cleft Op. with Ra. to neck.. | 1  |
| Treated elsewhere—no date .....        | 4  |

**"Laryngectomy.**—There were 7 patients who had total laryngectomy operations, one of these (case No. 175) although first seen at the Huntington Memorial Hospital, was operated on elsewhere. Three are living and well, one approximately 4 years and the other two, 3 years each, and 4 are dead. Of those dead, one survived 3 months, one 5 months, one 4 years and one 4 years and 10 months.

"The following is a brief detailed description of the patients who had a laryngectomy and are no longer living:

"(1) Case 136 was a male patient, aged 51, who had a bilateral involvement of the vocal cords in a papillary carcinoma. This is a very malignant form of neoplasm. His chief complaint was hoarseness of 8 months' duration. A total laryngectomy was performed, followed by external radium pack of 550 mc. hrs. The patient survived 3 months and died of pneumonia without any evidence of local recurrence. (2) Case 141 was a man, aged 54, with a tumor mass involving the right vocal band and cord with marked fixation. Although this patient was hoarse only 5 weeks prior to admission, there was a history of intermittent hoarseness over a period of years. The pathologist's report was Grade I cancer. A laryngectomy was performed and 2 years later a small gland in the neck appeared, which was removed, followed by x-ray treatment. He survived 4 years and 10 months following the laryngectomy and died of pulmonary hemorrhage. (3) Case 175 was a male, aged 47, who had a tumor of the left vocal cord of 6 months' duration. Biopsy report was Grade I cancer. A laryngectomy was performed elsewhere. This patient survived 4 years and 1 month and died of cancer of the stomach, with no evidence of local recurrence. (4) Case 178 was of the subglottic type and has already been described in detail.

"Of the 3 surviving patients (1) case No. 172 was a patient, aged 45, with involvement of the vocal cord (Rt.), anterior commissure and epiglottis. The duration of his symptoms prior to admission was 2 months. The tumor

was reported as Grade I from one part and Grade II from another section. The patient has been alive and well almost 4 years. (2) Case No. 176a was a patient, aged 54, with a tumor on the left vocal cord of 10 months' duration. The pathological report was epidermoid cancer Grade I. The patient has been alive and well approximately 3 years. This patient had diabetes of quite marked degree at the time of **operation** and was given diabetic treatment before and following the operation. He also had x-ray therapy following the operation. (3) Case No. 187 was a patient, aged 48, with a Grade II tumor on the left vocal cord and band of 2 years' duration. In addition to **laryngectomy**, he also had some **x-ray therapy** following the operation. He has been alive and well approximately 3 years.

"All the total laryngectomies were performed by the one-stage operation. A combination of the Gluck and Perier methods was employed, resecting the larynx from below upwards. The prelaryngeal muscles were resected in 2 cases. There were no operative mortalities in this series.

*"Laryngofissures or Hemilaryngectomy.*—In this series, there were 12 operations, 9 males and 3 females. Of these, 4 are living and well, one over 15 years, one 12 years and one 10 years and 5 years and 3 months without recurrence. Of the 8 dead, 1 died 4 years later of carcinoma of the stomach, there being no recurrence of the laryngeal cancer. Another patient, female, the youngest in the group, aged 20, had a hemilaryngectomy with a bilateral window resection and died 3½ years following operation. One case, No. 78, had an operation 10 years previously, suffered a recurrence and then died 13½ years after the original operation. The remaining two survived approximately 7 months. There was 1 operative death in this series. The patient died 4 days following the operation from pulmonary abscess. Laryngotomy with removal of the right vocal cord and part of the arytenoid was carried out in 1 case.

"In view of present experience, better results by more radical primary removal should be obtainable; more complete hemilaryngectomy and more frequent total laryngectomy.

*"Partial Operation with Irradiation.*—There were 21 patients in this series and for various reasons a major operation was not carried out. In some of these a more radical operation was either contraindicated because of the location and extent of the lesion or the patient declined operation. The prognosis in many of these patients was bad to start with and no hope of cure could be expected. Palliative relief was the most that could be expected and this was obtained in many cases.

"The procedure was to remove as much of the growth as possible, sometimes with the aid of **diathermy** and the implantation of **radium seeds** into the remainder of the growth or the region from which the growth was removed. There were 5 patients in this group who survived over 3 years as follows: 7 years, 9 months; 6½ years; 4 years, 3 months; and 2 patients 3½ years. One of these, case 24, had a bilateral **Harmer operation** plus **seed insertions**. The first two cases are of interest because of the comparatively long duration of survival and they are, therefore, described more in detail.

"The first patient is case No. 60 (H. H. No. 22-1131), a male, aged 60, admitted to the Huntington Hospital September, 1922, complaining of sore throat and hoarseness of 9 months' duration. A laryngoscopy was performed and a growth was found involving the false and true cords. A specimen was removed and 3 **radium seeds**, 2 to 3 mc. and 1 to 1.5 mc. were inserted into the growth. The report of the biopsy (Path. No. 23-86) was early epidermoid carcinoma arising in papilloma.

"January 17, 1923. — Laryngoscopy. — Considerable mass removed from region of the left true and false cord, anterior part, and from the subglottic portion of anterior wall of

Total mass was considerably greater than appeared under indirect laryngoscopy. Five seed 1.0 mc. each were inserted into base of growth at intervals of about 5 mm. October 22, 1930. Patient died at the Pondville Hospital. At autopsy, there was a recurrence of the tumor in the larynx with regional metastases. The pathologists' report (Path. No. 30-2693) showed epidermoid cancer. Grade I.

"This patient also had carcinoma of the stomach, but this was not the same tumor that was in the larynx and, therefore, not metastatic from the original lesion.

"The patient who survived 6½ years (case No. 55) was also a male, aged 65, who had complained of hoarseness for 6 or 7 years before coming to the hospital. His lesion involved the right vocal cord. The biopsy reported was carcinoma. This also began as a Papilloma. A tracheotomy was performed, followed by partial removal of the growth and radium seed insertion.

"The remaining patients in this group, although they survived less than 3 years, nevertheless, were considerably relieved from their suffering. Here, too, were patients who very likely would have fared much better with a more radical procedure, particularly in the cordal type of lesion.

*"Treatments with Radium Alone.—* There were 34 patients, most of whom (26) were of the extrinsic type. Many of these had metastatic glands at time of admission. The remaining 7 were of the intrinsic variety, and an operative procedure would no doubt have given better results, but for some special reason, radiation therapy was carried out. The patients in the earlier years were treated by means of the radium externally or with radium emanation seeds.

"The results obtained in the past by radium treatment alone are not particularly encouraging. It is striking to note that the intrinsic type in this series fared no better, and in many cases not so well as the extrinsic. This poor result may be accounted for by several factors:

1. radioresistance of the tumor cells;
2. the patients may have been debilitated

or alcoholic and such patients rarely show a good resistance to cancers or respond well to treatment; 3. inadequate dosage or improper distribution of radiation; 4. it has been observed that, occasionally, growths may be stimulated to greater activity when the dose employed is too small.

"The center of the growth may disappear, but the periphery having received insufficient dosage continues to proliferate. The best results in this series were obtained with the first irradiation treatment, when it was adequate. Subsequent treatments were not so effective, especially if applied too soon after the primary treatment, because it is known that previous treatments often make a cancer radioresistant. If the irradiation treatment is intensive, fear of radionecrosis is great, especially so in the larynx, since the cartilages are particularly vulnerable to this complication. Delayed burns have occurred years after treatment (8 years—Chevalier Jackson). Harmer believes it is due to progressive endarteritis obliterans following irradiation in excess of local tolerance of the tissues. This type occurs more commonly in the larynx than elsewhere.

"The best result was obtained in case No. 162, in spite of the fact that the lesion was an extensive one involving the epiglottis, the aryepiglottic fold and the pyriform sinus and the tumor was a Grade II, which is not particularly radiosensitive. The patient was relieved for 3 years. This may be explained on the basis of the relatively high dosage the patient received.

"There were 5 patients, each of whom survived 1 year and 4 months following treatment. The remaining patients were relieved approximately 6 months on the average. A tracheotomy was performed in 19 patients, in most cases preliminary to radiation. In a few cases, it be-

came urgent during or immediately following treatment. There was 1 death which occurred on the third day following the insertion of seeds.

*"Results of Treatment with Radium and X-ray.*—There were 40 patients in this series, some were of the intrinsic, but the greater number were of the extrinsic type. The results obtained here by the combined treatment show a decided improvement over the results of either radium or x-ray therapy alone. There were 12 patients in this group who were relieved and survived over 1 year.

"The best result was in case 64 (H. H. 22-1365), in a patient who lived 5½ years following the treatment by irradiation. Unfortunately, this was a clinical diagnosis, as no specimen was removed, but there appears to be no doubt as to this being anything but malignant. This was in a male, aged 66, who presented himself at the hospital with the complaint of a 'bunch in the throat, and hoarseness.' The patient further stated that 3 years ago he noticed a swelling in the left side of his neck which gave no symptoms except hypersensitiveness when taking hot foods. Prior to coming to the hospital, the patient consulted Dr. Abbott, in Providence, who referred the patient to Dr. D. C. Greene, who later referred him to the Huntington Memorial Hospital.

*Examination.*—Upon the laryngoscopic examination under ether anesthesia, the growth was found to involve the left lateral margin of the epiglottis, the aryepiglottic fold, the arytenoid and the false cord.

*"Treatment.*—5 to 1.5 millicurie seeds were inserted in different portions of the growth less than 1 cm. apart. The patient showed signs of dyspnea and became cyanotic, whereupon it became necessary to do a tracheotomy. This was carried out while the patient was still under ether anesthesia. His operation was done on November 8, 1922. In January, 1923, the patient received Roentgen treatment by Dr. Morrison.

"The patient remained well and was followed in the clinic until 1928 and on June 10, 1928, a letter was received from the Town Clerk stating that the patient died of carcinoma of the esophagus.

"A good result was obtained in Case No. 188. This was a male, aged 66, with a Grade 1

lesion in the right pyriform sinus. Ten seeds of 1 mc. each were inserted throughout the growth, followed by 5100 r. units of Roentgen therapy. This patient has been living and well for 3 years.

"Another (Case 96) survived 2 years, 10 months.

"Not unlike the previous group, most of these patients required tracheotomy prior to treatment.

"There was one death in this series. This occurred in a male patient of 77 who had seed implantation followed by Roentgen therapy. After the treatment, the patient began to have signs of dyspnea, an emergency tracheotomy was performed, and he died several days following operation.

*"Roentgen Therapy Only.*—The patients in this group were the most unfortunate, in that the disease had already extended widely and in practically all cases metastases were present.

"There were 37 patients in this group, of which 16 required a tracheotomy on admission. Three patients had gland dissections in addition to Roentgen therapy. One received surgical diathermy to the lesion in addition to x-ray. One patient had a positive Wassermann and, in addition to Roentgen therapy, was treated with potassium iodide. This patient survived 3 months, dying from hemorrhage due to cancer of the rectum. There were only 4 patients in this group who survived 1 year or over. The best result was in the patient (Case No. 184), who lived 1 year, 11 months following treatment, having received 6000 r. units, probably one of the largest dosage to date. The average duration of life following treatment in the remaining cases was 6 months.

"No Treatment.—There were 19 patients who received no treatment. In 12 of these the duration of life following the first visit is not known. Three of this group lived over 1 year. One patient, Case No. 102, was a man, aged 72, who had an early lesion on the right vocal cord which was still mobile. He refused treatment and survived 5½ years, finally dying from involvement of the esophagus. This illustrates an early intrinsic type of carcinoma of the larynx, its slow growth and finally the extension of the growth to involve the esophagus. The average life in the remaining cases was 5 months.

*"Complications.*—With the exception of cervical metastases, the most frequent complication was involvement of the

*esophagus*. This was present and recorded in 17 patients of whom 13 were in males and 4 in females. The ratio of postcricoid involvement in females is much greater than it is in males and for this reason, the incidence of esophagus complication in females is much higher. Death from *hemorrhage* occurred in 4 patients. *Pneumonia* accounted for 2 deaths following operation. *Mediastinal abscess* and *abscess of the throat*, 1 each. In 2 patients, *carcinoma of the stomach* is recorded as the cause of death, one 4 years and one 6½ years following treatment for cancer of the larynx. One patient died of carcinoma of the uterus 1 year and 2 months following treatment of the larynx.

"SUMMARY AND CONCLUSIONS. — 1. This series embraces 202 cases, 81 intrinsic and 101 extrinsic cases of cancer of the larynx. In 20 cases, the site was not stated.

"2. We recognize leukoplakia as a precancerous lesion, and that papilloma not infrequently undergoes malignant transformation.

"3. The relative infrequency of laryngeal cancer in females compared to males.

"4. The fifth decade of life shows the greatest incidence of cases.

"5. The triviality of the symptoms in proportion to the seriousness of the disease.

"6. The relatively slow course of intrinsic carcinoma and the relatively low-grade malignancy offers ample time for thorough surgical treatment with a good prognosis.

"7. It is our opinion that surgical removal of the growth in the early operative intrinsic type offers a good chance of permanent cure.

"8. The early diagnosis offers a patient his best chance of cure.

"9. In certain types of not entirely operable tumors, which are highly radio-sensitive, the combination of surgery and irradiation have produced good results.

"10. In the far-advanced cases of metastases, we rely entirely on irradiation for temporary relief.

"11. We feel that the treatment by irradiation, up until very recently, has been inadequate, and our entire conception of this method of treatment is being revised.

"12. Out of a total of 19 operative cases of proved cancer, 7 are living, and well, the longest duration 15½ years, the shortest 3 years, to date of publication.

"13. If it can be shown that radiotherapy can produce as high a percentage of permanent cures as surgery, it will be a safer method of treatment and will be welcomed by the surgeon and a blessing to the patient."

**NEW PROCEDURES.—Surgery.** —Granulations with subsequent reunion in the midline are the formidable hindrances to successful treatment of *webs of the larynx* surgically. It is therefore of interest to note an idea presented by S. Iglauer (Arch. Otolaryng. 22: 597 (Nov.) 1935) which may serve the laryngologist well. The principle is derived by analogy from its use in the 2-stage operation sometimes employed by the general surgeon for the treatment of syndactylism. This consists in passing a wire through the proximal portion of the web between the fingers and leaving the wire in place until the epithelium has grown through from both surfaces, forming a new commissure. At the second operation the web between the fingers is completely divided, the epithelium-lined commissure preventing adhesions from reforming. In employing this method, Iglauer used a spring ring (from a watch chain) to which a long

piece of thin copper wire had been soldered, was held open by a laryngeal forceps and inserted through the puncture. The spring was then released, closing the ring. The attached wire was brought out through the pharynx and nose. A piece of rubber tubing was slid over the wire, which was held in place with adhesive plaster attached to the cheek.

originally planned. Within limits, the longer the ring can be retained, the better the chances of obtaining an epithelium-lined commissure, which is essential for the success of this procedure. If I repeat this operation on another patient, I shall allow the ring to remain in the larynx for about 3 weeks and shall use a piece of braided silk instead of wire to anchor the ring. This will be

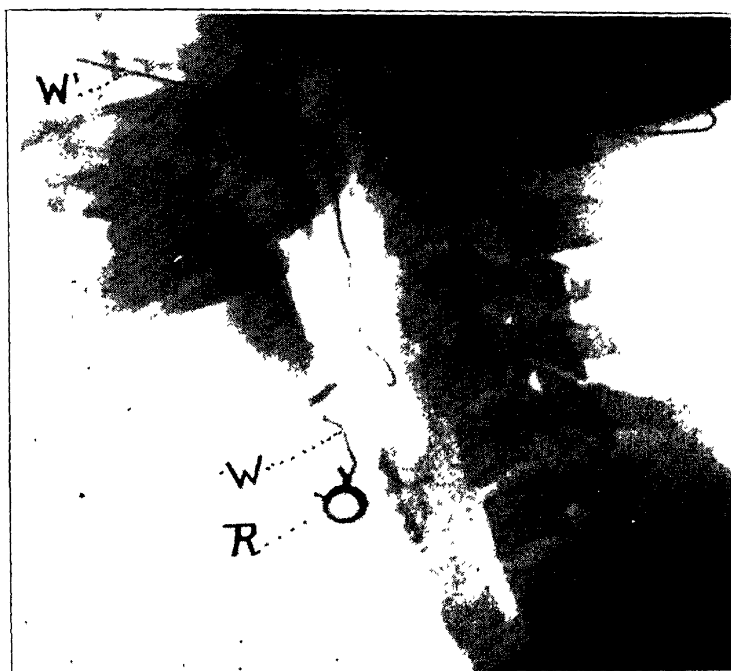


Fig. 1.—Lateral roentgenogram showing spring ring anchored in laryngeal web. R indicates the ring;  $WW'$ , the wire. (Iglauer: Arch. Otolaryng.)

During the following week the patient complained of some soreness in the throat, occasional gagging, a slight cough, and some difficulty in swallowing. On the first post-operative day an x-ray picture of the neck was taken. This showed the ring in good position within the larynx, but the wire had broken (Fig. 1). It therefore became necessary to remove the ring. This was done the following morning, at which time the second operation was performed. Iglauer concludes, "the breaking of the wire attached to the ring rendered it necessary to remove the latter before the time

more comfortable for the patient. It is questionable whether the ring technic could be carried out on an infant without resorting to tracheotomy as an adjuvant." It is not so important that this first attempt is reported despite its small success resulting from a too early removal of the ring before complete epithelialization around it had occurred. This method deserves a good trial.

**ARTIFICIAL LARYNX.**—The greatest catastrophe to the patient who has been confronted with the necessity of having his or her larynx removed is not so much the fact that cancer exists;

those who have seen these patients have become familiar with their chief concern, *viz.*, the loss of voice. To be placed in such a status was to be made irreconcilable to life. The surgeon has been able to give a good prognosis, in so far as life itself is concerned. But, until a few years ago, the best that could be offered to replace that lost organ—so essential for social and economic happiness—was a pseudo, or esophageal, voice. Further, even though such a patient finally succeeded in establishing an esophageal voice, such success followed only after much hardship and self education. In view of that situation, the perfection of the artificial larynx is nothing short of being miraculous. The laryngectomized patient may expect to talk, and this even over the telephone, within a week after the tracheotomy wound has healed. Little or no unusual effort need be expended. C. Sheard (Eye, Ear, Nose and Throat Monthly 15:96 (Apr.) 1936; reprinted from Proc. Staff Meet. of Mayo Clin. 6:253 (Apr. 29) 1931) has permitted a republication of his report on the pioneer work carried out in the Bell Telephone laboratories in 1931. At this time, the instrument is practically a perfect one. The following principles still apply:

The pitch of the voice when the vowels are spoken varies, but corresponds to about 90 cycles each second for a deep-voiced man to 300 cycles each second for a high, shrill-voiced woman. The average pitch for woman is near middle C or 256 cycles each second, and for man it is approximately half that number, or about 125 cycles each second. The pressure of air in the trachea necessary to the production of voice is, for a tone of ordinary pitch and loudness, between 150 and 250 mm. of water, whereas in loud shouting the pressure rises to about 1000 mm. of water.

All voiced sounds pass through 2 variable resonating cavities, the throat and the mouth. For this reason, all such sounds are characterized by component frequencies being magnified in 2 particular regions. In any of the voiced sounds, it is the modulation of the cord tone that gives the distinctive sound rather than the characteristic of the vocal cords. The latter determines the type of voice and identifies the person who is talking. The experience of various investigators, particularly those of the research department and the engineers of the Bell Telephone laboratories, with persons who have lost their larynges through operation, has emphasized the fact that the differentiation of speech sounds is accomplished practically by the positions of the mouth and lips and that the sounds from the vocal cords act only as carriers.

*Artificial Larynx.*—So far as we are aware, the first artificial voice box in this country was developed a few years ago by the laboratories of the Bell Telephone Company. Another and more expensive instrument (patented in 1927) then appeared on the market. Both instruments are of the fixed reed type, differing fundamentally in mechanical construction, details of assemblage, and adjustment. In both the first type of Bell Telephone artificial larynx and in the so-called McKesson instrument the reed is made of thin and easily flexed or nonresilient rubber. Both ends of the vibrating reed are fastened to a suitable holder and the tension on the strip of rubber is regulated until the apparatus is in adjustment for use as a voice box. These earlier instruments have proved more or less unsatisfactory to the users because of the frequent necessity of adjustment of the reed, breakage of reeds, inconstancy of pitch, inoperability (through jamming) when loud speaking is attempted and, in general, in-



ability to carry on conversation in a reasonably subdued tone of voice. These physical handicaps produced uncertainty of operation of instruments, with the resultant lack of assurance on the part of the users. In 1930 and 1931 there was developed in the Bell Telephone laboratories and marketed through the Western Electric Company a number of 2-A artificial larynx in which improve-

damaged in cleaning. The instrument which has been developed we believe meets the requirements in large measure.

"The essential parts of this artificial larynx, which is being used by 32 persons on whom laryngectomy was performed are shown in Fig. 2. Parts 1 and 4 constitute the box proper. The upper portion of the tube 4 is threaded to receive the cap 1. The portion 4 of

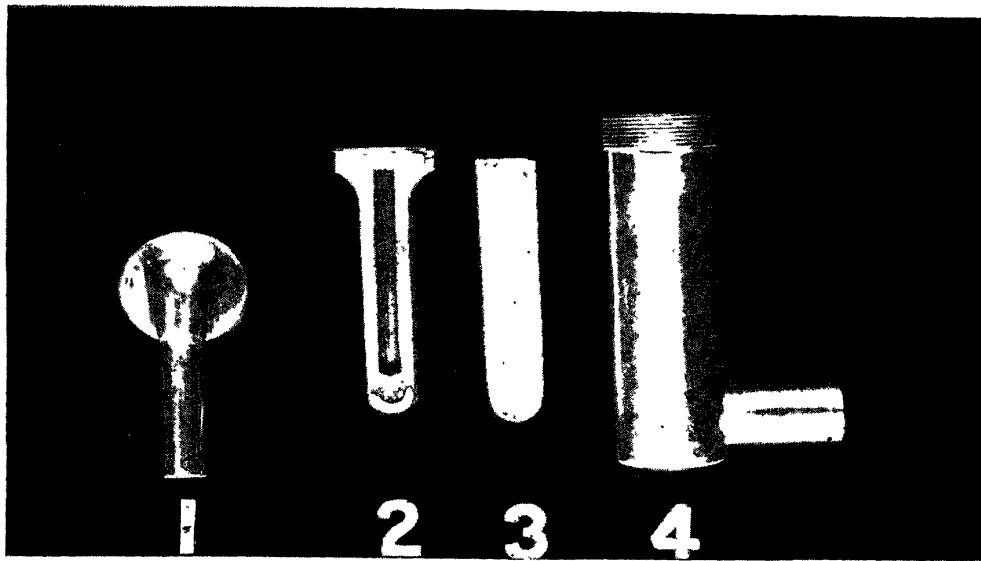


Fig. 2.—1. Upper portion of instrument to which is attached the rubber tube for insertion in the mouth. 2. Reed holder which is clipped into tube (4). 3. Reed of hard rubber. 4. Lower portion of instrument to which is attached connection to neck. (Sheard: Eye, Ear, Nose and Throat Monthly.)

ment was made in many of the particulars which have been stated in the foregoing recital of criticisms.

*"A New, Simple Type of Artificial Voice Box.*—In the spring of 1930 we commenced, in our physical laboratories at the clinic, the development of a type of artificial larynx which would operate, so far as the instrument was concerned, at all times and under all circumstances (such as that of freezing weather), would permit of ordinary or loud speaking, would possess a given fundamental pitch or frequency which could be made as high or as low as desired, and which could be reproduced by replacement of the reed in case the reed was broken or

the voice box also has an opening of about  $\frac{1}{4}$  inch in diameter situated near the top. This opening is thumbbed by the user when he talks. It serves as an aperture for the passage of air into the tube, and thence through the voice box proper and its accessory attachments to the tracheotomy cannula or opening when the user desires to breathe. The reed holder 2, with a groove or channel for the passage of air from the lungs to the mouth, carries the reed 3. The reed holder is so constructed that it slips into the metallic case 4 and rests on its upper edge.

"In such investigations as these one might be concerned with two kinds of

reeds, namely, free reeds like those in the harmonium and beating reeds which are too large to pass into the opening with which they are associated. In this instrument, the reed, which is preferably of hard rubber about 0.1015 in. thick, is wider than the groove or air channel carried by the reed holder and is, therefore, a beating reed. The curvature of the face of the holder on which the reed beats is not uniform. It is flat for ap-

top to bottom along its length in such a manner as to afford the maximal volume of air for minimal pressure when the instrument is in use as a voice box.

"The tone of the voice or the frequency of the vibrating reed is regulated by the length of the reed. Exact duplicates of any given length of reed which has been found satisfactory to the patient can be made readily, thus

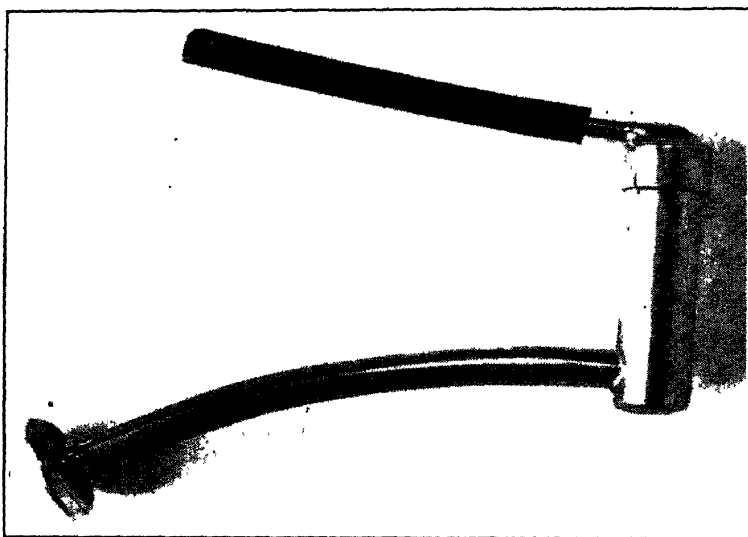


Fig. 3.—Ensemble of artificial larynx and one type of breathing and vocal attachment. (Sheard: Eye, Ear, Nose and Throat Monthly.)

proximately  $\frac{1}{4}$  in. from the point of insertion of the reed. The curvature thereafter is continuously increased until the extremity of the holder is reached. With this contour, the resilient reed can bend so as to close down in a smooth and flat manner and thus progressively cut off the air passage from the base or fixed end to the free end. As the closure proceeds, it does so with certainty and uniformity. The reed in operation, therefore, closes the opening into the holder with a gradual or rolling action, thereby further eliminating the harshness of quality consequent on sudden discontinuity.

"The groove in the holder is about  $\frac{3}{16}$  in. wide and its depth is graduated from

insuring rapid replacement of the reed when required (as in breakage in cleaning, curling, etc.) and affording continued use of the instrument without the necessity of adjustment for either operation or regulation of the pitch of the voice. In this manner, the fundamental or basic tone quality of the voice can be determined and maintained indefinitely and, since the pitch of the voiced tones can be made as high or as low as desired, each patient can be fitted with an artificial larynx that possesses the pitch or tone desired.

*"Use of Artificial Voice Box.*—In case a tracheotomy tube is required, attachment of the artificial larynx to the tube can be made by a suitable metallic

ferrule, which, at one end fits into the tracheotomy tube, and at the other end is slipped into a piece of rather stiff rubber tubing of a length such that the voice box is in proper position for use.

"Fig. 3 shows an ensemble which has been used frequently and satisfactorily by patients who do not make continuous use of tracheotomy tubes. The placement at the neck is secured through the use of a rather shallow metallic cup large enough to cover adequately the tracheal opening. The cupped disk is attached to a metal tube, which, in turn, is so bent and adjusted that the disk is placed readily in proper position at the neck as the soft rubber tube (attached to the upper portion of the voice box) is slipped into the mouth. (Fig. 4.) The user can carry this artificial larynx in a pocket, so that it can be picked up readily, applied to the neck and used for speech *ad libitum*. The positioning of the instrument, pressure against the neck, and removal of the instrument from the neck when not in use as a voice box can be regulated by the user. This ensemble is shown in use in Fig. 5 and serves as an illustration of one of the several ways in which the artificial larynx may be adjusted and fitted to meet the patient's requirements.

"Experience has demonstrated that every individual needing an artificial voice box is a law unto himself. The physical or anatomic characteristics of the face and neck, the shape and size of the tracheotomy opening, the presence or absence of a tracheotomy tube, etc., modify considerably the mode of attachment or placement of the voice box to the neck. The length of rubber tubing for insertion in the mouth, and the number and character of notched openings in the portion of the rubber tube placed in the mouth are also matters of importance and are determined only by trial and adjustment. Articulation

is much improved in general if the rubber tube is placed in the mouth between the teeth and toward one cheek and as far back as possible. The matter of the training of the subject to talk is reasonably simple, but slowness of speech, attempts at distinctness of pronunciation and suppression of a per-



Fig. 4—Artificial voice box in use, showing placement at neck and position of tube in mouth. (Sheard. Eye, Ear, Nose and Throat Monthly.)

fectly natural desire to talk loudly must be impressed on the memory of the user."

**BRONCHOSCOPY.**—Objection to the term "asthmatoïd wheeze" is properly made by L. H. Clerf (Ann. Int. Med. 9: 1050 (Feb.) 1936). The reasons for this are obvious when merely Clerf's few case reports of "asthmatoïd wheezing" are considered, which proved on more thorough examination by means of the bronchoscope to be almost everything else but asthmatic in origin. For example, one case presented a carcinomatous mass in the left bronchus; another was cured following the removal of a button from the cervical esophagus.

**Bronchial Asthma.**—The noteworthy *bronchoscopic findings* in cases of true bronchial asthma are collapse of the trachea and bronchi during cough and forced expiration, and the presence of abnormal secretions. L. H. Clerf (*Ibid.*) adequately describes the picture: "Moderate forward bulging of the membranous wall of the trachea during cough is often observed in children, occasionally in adults, and is not considered pathologic. In the normal person there is a rhythmic movement of the trachea

and bronchi during respiration. The collapse is undoubtedly passive in nature, and the impression is gained that the tracheal and bronchial walls are being forced shut by some external influence. While not absolutely characteristic of the average case of asthma, it is unquestionably a pathologic state that is present in certain of the different conditions clinically described as asthma.

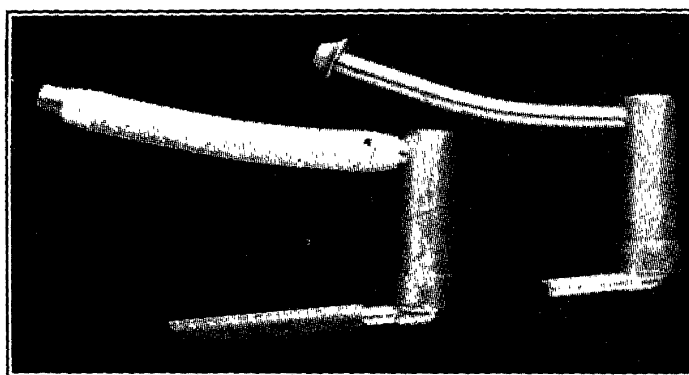


Fig. 5.—Ensembles showing other types of breathing and vocal attachment. (Sheard: Eye, Ear, Nose and Throat Monthly.)

and bronchi during respiration. The bronchi elongate and dilate during inspiration; during expiration they shorten and contract. These changes are participated in by the entire bronchial tree. The collapse observed in certain cases of asthma differs from the normal phenomenon, both in appearance and in the mechanism involved in its production. At the beginning of expiration in many cases there is noted marked collapse of the trachea. In some, the collapse is limited to the posterior tracheal wall, which, bulging forward, becomes convex and fits into the concavity of the anterior wall of the trachea; the resulting lumen is crescentic. The forward bulging occurs during expiration and cough, and is in proportion to the force of the expiratory effort. Occasionally the lat-

eral tracheal walls also participate in the collapse, giving the lumen a triangular appearance. The lumen promptly returns to its normal more or less rounded appearance at the beginning of inspiration. In many of these cases there is an associated collapse of the walls of the bronchi, including the orifices of the bronchial subdivisions. These changes are often sufficiently marked to interfere with the introduction of the bronchoscope, which can be advanced only during inspiration. This is not

**Treatment.**—**Vaccines** made from secretions obtained through the bronchoscope offer some additional means for treating bronchial asthma. Particularly should this type of therapy be utilized when bacterial allergy is shown to be the underlying factor. Again, Clerf voices the trend of today in his conclusion that bronchoscopy should be given a trial in the treatment of cases

of bronchial asthmas that do not respond to commonly employed methods. "The best results are secured in cases with tracheobronchitis, excessive secretions or bronchial obstruction."

**LIPIODOL.**—Needless to repeat, lipiodol is invaluable in all x-ray studies of organs which permit its use.

***Bilateral Apical Nontuberculous Bronchiectasis.***—J. Steidl and F. H. Heise (Am. Rev. Tuber. 33:61 (Jan.) 1936) report an interesting case for diagnosis, in that a protracted number of

pulmonary symptoms were demonstrated definitely by the use of lipiodol to be caused by upper lobe bronchiectasis—a most unusual combination of site and pathology. The authors consider the possibility of a cystic upper lobe on the right side because of the good filling with oil and a bronchiectatic (nontuberculous) upper lobe on the left side because of the poor filling with oil. The patient, female, aged 28, finally succumbed suddenly of pneumonia. Full details were not available.

## DERMATOLOGY

By JOHN B. LUDY, A.M., M.D.

### ACANTHOSIS NIGRICANS.—

**Treatment.**—B. Strandell (Acta Med. Scandinav. 87:551 (Feb. 18) 1936) reports the successful treatment of acanthosis nigricans with **intragluteal injections** of a potent **liver extract**. In view of the fact that acanthosis nigricans heretofore could not be improved by internal treatment, the author considers his observations on 2 patients treated with liver extract of interest. He considers it possible that there are certain relations between acanthosis nigricans and the gastrohepatic physiology.

### ACNE VULGARIS.—*Pathogenesis.*

—T. Rosenthal and T. Neustaedter (Arch. Derm. and Syph. 32:560 (Oct.) 1935) believe that associated with acne there exists an abnormality of formation or of utilization of the sex hormone. In their study of 29 cases they conclude that a definite relationship exists and that a deficient secretion of the follicle-ripening hormone may prove to be the direct or indirect factor in the cause of one type of acne. In the course of routine filtered x-ray therapy in the treatment of acne it is conceivable that the pituitary gland is affected by the relatively low dosage of irradiation administered and in consequence induces a normal ovarian response.

**Prophylaxis and Treatment.**—Acne vulgaris may to a large degree be prevented during the period of adolescence by keeping the skin of the face dry and rather chapped, according to S. Nichols. The use of **soap** and the daily application of **lotio alba** is recommended until the age of 15 is reached.

(814)

To keep the skin dry, the face is **washed** before going to bed with **castile soap and hot water**; then well sopped for 5 minutes with **lotio alba** one-fourth strength. This treatment is continued until the skin is dry and chapped.

There are 2 classes of acne, *i. e.*, the systemic and the local, as pointed out by D. J. Wilson. The physician cannot treat successfully the majority of acne cases unless he has the full coöperation of the patient. With juvenile cases, it is necessary to have the support of the parents.

Systemic treatment is as follows: The diet must be controlled, *i. e.*, no pastry, minimum of fats, candies, chocolate, sundaes, jams, jellies, preserves; pork or gravies are not permitted. A minimum of white and rye bread, biscuits, potatoes, macaroni, cheese and nuts may be allowed. Alcohol is contraindicated. When the acne is under control, the diet may be more liberal.

**Constipation** must be corrected, and for this, usually 3 glasses of **water before breakfast**, going to the stool immediately after breakfast with the full determination to have **complete evacuation**, should be helpful. Occasionally, if the constipation is severe, some **laxative** in diminishing doses is necessary. **Fluid extract of cascara**, as a rule, works well and may be followed by diminishing doses of a **mineral oil-agar preparation**, preferably without phenolphthalein.

For patients who have a moderate **anemia**, **Fowler's solution** or the **cacodylates** may be prescribed. In severe cases, **liver extract** may be used.

Bromides and iodides should not be used and iodized salt is to be discontinued.

Although occasionally **vaccines** give good results, they are ordinarily unreliable.

Practically every patient with acne vulgaris also has *dandruff*. Unless the scalp condition is properly treated, the acne returns after an apparent cure. When starting antiseborrhea treatment, the **scalp** should be thoroughly **washed** twice a week with a stimulating **tar soap**. After 2 or 4 washings, once a week will be sufficient. The **hair** should be **brushed** with a stiff bristle brush for at least 5 minutes each day. This mechanically removes some of the liquid sebum from the scalp and distributes it along the shaft of the hair, thus diminishing scaling. After the hair and scalp are thoroughly washed, a rinsing of hot water followed by cold is advised. A turkish towel with a moderate amount of **massage** may be used for drying and a good **hair tonic** used each day.

The following formula is very satisfactory:

℞ *Hydrargyri*  
*chlor-corros* ..... gr. iiii (0.2 Gm.)  
*Resorcini* ..... ℥ii (60.0 Gm.)  
*Acidi salicylici* ..... ℥ss (15.0 Gm.)  
*Glycerini* ..... fl℥ss (15.0 c.c.)  
*Ol bay* ..... ℥ iv (0.24 c.c.)  
*Sp. vini rectific.*, 70%  
 q.s. ad. .... fl℥viii (240.0 c.c.)

**Ultraviolet irradiations** over the entire body, as well as locally, are valuable, particularly in young patients and especially if pus is present.

Since all papules and pustules are secondary to the comedo, it is clear that if the **comedones** are all **removed** there will be no secondary lesions. Many dermatologists insist on doing this operation themselves; however, it is rare when some member of the family cannot be found who will do it just as well. Comedones, papules and small pustules

can be taken care of in this way. Small lesions are often converted into large indurated ones if the work is too vigorously done, and a comedo which is resistant to moderate pressure should be left alone after the first attempt. After 2 or 3 days it will usually respond to an attack.

**Hot and cold packs** are valuable. They should be given as follows: (a) A turkish towel is wrung from hot water and applied to the face for 2 to 5 minutes by the clock; the time depends upon the type of skin, the type of eruption and the physician's experience. (b) The comedones are removed as previously directed. (c) The *débris* remaining on the surface is removed when the face is thoroughly washed with soap and water and a rough cloth. At first a mild soap is used and, as the skin becomes harder to chap, tincture of green soap and even surgeon's soap may be used. (d) After drying, the entire face is gone over by squeezing it firmly between the thumb and forefinger. This squeezes onto the surface much liquid content of the sebaceous glands which prevents it from hardening and forming comedones. (e) A fat solvent, such as carbone tetrachloride or equal parts of alcohol and ether, may now be sponged on the face, or soap and water may again be used and rinsed off with hot water. (f) Cold packs are now applied for 2 or 3 minutes. Ice is not advisable. (g) After drying, Duhrings' lotio alba:

℞ *Zinci sulphatis*  
*Potassi sulphuret*... āā 3i (4.0 Gm.)  
*Glycerini* ..... ℥ss (6.0 Gm.)  
*Aq. rosæ*, q.s. ad. .... ℥iv (120.0 c.c.)

is applied. If a stronger application is desired, Kummerfeld's lotion may be used:

℞ *Sulphuris præcipitati*.. 3i (4.0 Gm.)  
*Pulv. camphoræ* ..... gr. x (0.65 Gm.)  
*Pulv. tragacanthæ* .... gr. xx (1.3 Gm.)  
*Liq. calcis*,  
*Aq. rosæ* ..... āā fl℥ii (60.0 c.c.)

(h) If creams have been used previously as a "cleansing agent," the above schedule should be carried out only once a day at first and later increased to twice a day. Severe chapping is not desired and if such occurs, the applications are discontinued for a day or two. Pitting and scarring may be markedly diminished by exfoliating doses of **ultra-violet rays** following in as close succession as reactions will permit.

About 60 to 65 per cent. of average cases will be cured in from 6 to 24 months by the above method.

More poor results in the cure of acne are due to the failure to treat the concurrent seborrhea and a failure to remove the comedones than to any other cause.

**X-rays.**—Most general physicians are not equipped to give x-ray treatment. Although it is considered by far the most valuable single therapeutic agent available for the treatment of acne, it should be given by the specialists.

Many dermatologists have favorite combinations which from experience they have found to be of value. Darier prepared the following compound which is considered practical not only for the skin but for the scalp:

|                                 |              |
|---------------------------------|--------------|
| <i>Powdered soap</i> .....      | 40 per cent. |
| <i>Lard</i> .....               | 40 per cent. |
| <i>Oil of almonds</i> .....     | 20 per cent. |
| <i>Essence of geranium</i> .... | 4 drops      |

This soap mixture may also be used for the treatment of acne. There is no question that the use of soap as a local agent is necessary in the treatment of acne; the disadvantage of most soaps is that they are so irritating when applied directly to the skin that they are frequently discarded by patients who should use them. To overcome these disadvantages, the following formula was prepared; the prescription has the advantages of the soap mixture but none of its irritating qualities:

|                                |              |
|--------------------------------|--------------|
| <i>Stearic acid</i> .....      | 20 per cent. |
| <i>Liquid petrolatum</i> ..... | 5 per cent.  |
| <i>Triethanolamine</i> .....   | 5 per cent.  |
| <i>Cocoonut oil soap</i> ..... | 40 per cent. |
| <i>Distilled water</i> .....   | 25 per cent. |
| <i>Glycerin</i> .....          | 5 per cent.  |

It is made in the following manner:

Heat the stearic acid, liquid petrolatum and triethanolamine to 85° C. in a porcelain or glass container. Heat the distilled water and the glycerin to 85° C. in a separate porcelain or glass container. Maintain the heat at 85° C. and dissolve the cocoonut oil soap by agitation. Add the aqueous solution to the stearic acid mixture with slow but constant stirring. Remove the mixture from the source of heat and continue stirring until it is cool. Do not beat air into the cream.

The result is a smooth, pleasant mass which does not separate even in summer and which gives a good lather when mixed with water.

A. Skutta (Dermat. Wchnschr. 102: 137 (Feb. 1) 1936) believes acne vulgaris is greatly influenced by local conditions. He shows that the obstruction of the sebaceous glands (comedo) is the cause of the local symptoms. In view of the mechanical nature of this process, a mechanical therapy seems indicated, which formerly was effected chiefly by means of expression, and for this purpose the author has devised a **suction cup**. He used different types of cups for the removal of comedones and for the treatment of inflammatory manifestations. The suction apparatus can be operated with the water vacuum pump or with an electric pump. In addition to the local suction treatment, the author employs **general constitutional measures**. Three years of experience with the combined suction and general treatment have shown that it produces good results and reduces the cosmetic defects associated with acne vulgaris.

G. M. Crawford and J. H. Swartz (Arch. Dermat. and Syph. 33:1035 (June) 1936) hospitalized 10 patients with severe pustular acne and showed



their blood sugar content to be in the lower range of the normal at all times. They also found normal reactions to dextrose tolerance tests.

These patients were given a diet rich in **carbohydrates** and daily intravenous injections of **dextrose** for 2 weeks. Half of the patients showed a definite improvement, 20 per cent. slight improvement, and none were worse. Continuance of this diet over periods up to one year has resulted in continued improvement in 50 per cent. of the patients.

These results definitely intimate that a high carbohydrate regimen is not inimical to the welfare of patients with acne vulgaris.

**DERMATITIS. — ARSPHENAMINE DERMATITIS. — *Prophylaxis and Treatment.***—Most cases of frank arsphenamine dermatitis present warning signs before generalized dermatitis begins, according to L. W. Shaffer. warning signs before generalized dermatitis can probably be stopped before it gets a start.

Early prodromal cases offer a different problem than those showing frank exfoliative dermatitis. In most early cases treatment with arsphenamine may be guardedly continued by changing to a different type of arsenical, small doses, etc., until further sensitivity is determined. It is probable that a true allergic state does not develop in these early cases if treatment is stopped.

The addition of various substances to the arsphenamine to render it less toxic would be well suited to this type of case. **Physiologic solution of sodium chloride, dextrose, gelatin, sodium thiosulphate and calcium** have all been recommended for this purpose.

Another preventive measure of which there is little definite knowledge is **diet**. It has been shown that the presence of

carbohydrates in rats materially increased the tolerance to arsphenamine, which observation requires standardization of the diets of rats used in toxicologic tests on arsphenamine.

In some clinics the patients receive 2 or 3 tablespoonfuls of **dextrose** from  $\frac{1}{2}$  to 2 hours before treatment and it is thought to reduce reactions materially. **Sodium thiosulphate** has recently been the only popular detoxicating agent used as an adjuvant to the commonly employed methods of treatment. Clinical experience has proved that sodium thiosulphate is a valuable detoxicating agent for heavy metals, for arsenic in particular. Its value lies in its use early in the disease. After damage from arsenic has taken place, thiosulphate in any amount will fail to hasten the resolution of arsphenamine dermatitis. Sodium thiosulphate should, therefore, be given at the earliest possible moment. It is recommended that 1 Gm. (15 grains) of the freshly prepared solution be given intravenously at daily intervals for from 2 to 6 doses. A smaller dosage at the start is in line with the view that large doses would cause too rapid elimination, or freeing of arsenic from the tissues, with subsequent exacerbation of symptoms. Sodium thiosulphate has a tendency to produce alkalosis, so that it should not be continued indefinitely.

Recent articles announce surprisingly good results in the treatment of post-arsphenamine dermatitis from injections of **liver extract**.

The influence of treatment with liver in severe cases of arsphenamine dermatitis is soon apparent in definitely improved spirits and appetite, a decrease in temperature, and in marked skin improvement. In experimental animals with severe intoxication from arsphenamine, with great emaciation and even prostration, great improvement followed

injections of liver extract in from 1 to 2 hours. In man, intramuscular injections of liver extract are painless and are given 3 times weekly in doses of from 5 to 10 c.c. ( $1\frac{1}{4}$  to  $2\frac{1}{2}$  drams). Liver extract may also be given by mouth.

In cases of mild dermatitis, treatment with arsphenamine can be continued in conjunction with liver extract without skin manifestations.

The use of calcium in arsphenamine therapy is recommended by Gerwig. Neoarsphenamine dissolved in 10 c.c. ( $2\frac{1}{2}$  drams) of a 10 per cent. solution of **calcium gluconate** prevents nitritoid crises, delayed fever, malaise. A conservation dosage calls for 10 c.c. ( $2\frac{1}{2}$  drams) of a 10 per cent. solution of calcium gluconate intravenously and from 1 to 2 tablespoonfuls 3 times daily by mouth.

The use of **dextrose** in solution of from 2 to 10 per cent. as a dilutant for arsphenamine has been recommended by several investigators to prevent arsphenamine reactions, as well as its use by mouth preceding the injection. Arsenic combines with dextrose to form glucosides which are less toxic, which have a tendency to remain in the blood stream over a longer period, and which are excreted more rapidly.

The author proposes to treat any new patient of *postarsphenamine dermatitis* (nondiabetic) having accessible veins with 1 Gm. (15 grains) of **sodium thiosulphate** and 50 c.c. ( $1\frac{2}{3}$  ounces) of a 50 per cent. solution of **dextrose** injected intravenously daily for from 3 to 5 days. The administration of dextrose should be followed in  $\frac{1}{2}$  hour by 5 units of **insulin**.

Patients in whom venipuncture is difficult or impossible are treated with **liver extract** by intramuscular injection or with **calcium gluconate**.

**RADIODERMATITIS.** — *Treatment.*—A simple technic advocated by M. Craps and A. Alechinsky consists in **protecting the healthy tissues** with a screen of linen, pomade or tissue paper, and painting the lesion lightly with a 5 per cent. aqueous solution of **silver nitrate** has been recommended. In some cases to insure adherence to the solution and to facilitate its absorption, it is advantageous first to **wash** the affected area **with ether** and it is often necessary to clear the skin of squamas or less adherent crusts before application of the solution. The area is then exposed to a **quartz lamp** at an optimal distance of 20 cm. The period of irradiation varies from 5 to 10 minutes. In all cases it must be sufficient to produce complete drying of the solution and blackening of the area. If the color is not dark enough, the area is repainted until it becomes a glistening black. Since drying of the lesion begins from the time of the first application, the area treated should be covered only with a sterilized gauze compress. No fatty substances should be applied in the course of treatment. The patient is treated every other day.

H. Bordier (*Strahlentherapie* 56:205 (June 20) 1936) discusses the dermatitides and their malignant complications that occur in workers with x-rays and radium or after treatment with these rays. He points out that numerous antiseptic preparations were tried but have failed. The results with remedies intended to influence nutrition likewise failed to come up to expectations. Bocker suggested the use of **infra-red rays** and obtained favorable effects with these rays in 2 cases of ray dermatitis. The author, however, prefers **diathermy**, calling attention to the favorable effect exerted by the high frequency currents on the trophic disturbances in the tissues.

If the ray dermatitis is in a region in which the tissues consist largely of fat (abdomen) and the circulation of the humors is deficient, with impairment of vitality of the tissues, the treatment must aim at increasing the vitality by stimulating the circulation of blood and lymph fluid in the region of the ulceration. Diathermy exerts a hyperemic action not only in the region of the ulceration, but also in the tissues underneath. A lead electrode is applied 3 or 4 cm. from the edge of the ulcer. A second electrode is applied on the other side of the ulcer, so that the high frequency current passes through the tissues under the ulcer. The treatments are applied in series of 12 or 15 sessions. The intervals between the sessions differ from case to case, but the interval between the series does not exceed a month.

For the ray dermatitides that develop in tissues that have little fat (face, hand, leg, etc.), the author recommends **coagulation by diathermy**, the aim being to destroy the tissues that have been injured by the rays. Following the coagulation, he applies gauze **compresses** saturated with 1 per cent. **phenol**. The bandages are changed daily.

For the ray dermatitides that assume a malignant character, the author likewise recommends **coagulation by diathermy**. He employed it for 25 radiologists who suffered from malignant degeneration of keratotic fields. He cites passages from some of the reports written by the radiologists themselves.

**STREPTOCOCCIC DERMATITIS.—Differential Diagnosis.**—J. Kinnear (Brit. J. Dermat. 48:173 (Apr.) 1936) asserts that until recently, the streptococci causing impetigo and streptococcic dermatitis have not been differentiated, and in view of the marked

differences between the clinical appearances of these diseases, this has led many to reject the streptococcic origin of the latter. The active stage of streptococcic dermatitis is characteristic. The red, glazed area with its abundant exudation of serum from the whole surface is quite easily distinguished from both eczema and other forms of dermatitis. The less active phase of the disease, streptococcic pityriasis, is also characteristic. The scaling is a fine lamellar exfoliation and may be profuse. Occasionally this stage of pityriasis is the primary stage of the disease without a preceding dermatitis; frequently, when the scalp is acutely involved, patches of dry pityriasis are found on the body; but it is most commonly found as the active stage is passing and is almost invariably at the margins of an acute lesion, especially on the scalp, above an intertrigo behind the ear. All gradations between these two phases may be found, frequently in the same patient in different parts of the lesion. Streptococcic dermatitis attacks the folds of the skin and spreads from the folds to the neighboring skin and, as the disease is brought under control, it gradually contracts till again the folds alone are affected. Impetigo has not the same tendency to affect the folds. The lesions of impetigo are comparatively small, and when a large area is affected, it may be seen that it is by numerous distinct elements. On the other hand, the continuity of the lesion in streptococcic dermatitis is evident. Vesicle formation such as occurs in impetigo is absent in streptococcic dermatitis. As a rule, it is not difficult to distinguish streptococcic from other forms of intertrigo. The extent of this streptococcic infection may vary from a tiny lesion at the upper end of the retro-auricular fold to a generalized involvement of the whole surface of the body. It may disappear

spontaneously in a few days or last for years.

For *treatment* during the acute stage, a **nonirritating antiseptic in solution** is best. In the less active stage, **coal tar** is invaluable. The causal organisms of impetigo and of streptococcic dermatitis are entirely different types of streptococci. The author found that a hemolytic streptococcus could be isolated, from impetigo, whereas from streptococcic dermatitis an anhemolytic streptococcus was obtained. In cases of a mixed type, both streptococci were found.

#### DERMATITIS VENENATA.—

**Prophylaxis.**—J. M. Blank and A. F. Coca (J. Allergy 7:552 (Sept.) 1936) made a suitably controlled study of injections of **poison ivy extract** on the incidence of ivy dermatitis in the C. C. C. Veterans Camp MC-64, Morristown, N. J. The men spent their active working days in areas which abound with the poison ivy and poison sumac plants, and contacts were unavoidable. The exposed men, all working under approximately the same conditions, in areas contaminated with ivy and sumac, were to be listed in three groups: (1) to receive 4 injections, at weekly intervals, of 0.5 c.c. (8 minims) of almond oil containing 10 per cent. by volume of acetone and 0.1 per cent. of solids extracted from poison ivy leaves with acetone and freed from chlorophyll; (2) to receive 4 weekly injections of 1 c.c. (16 minims) of a similar extract containing 0.66 per cent. of the poison ivy solids; and (3) to receive no prophylactic injections.

As the men presented themselves with ivy dermatitis, they were to be treated in rotation with the two extracts and almond oil containing 10 per cent. of acetone.

The prophylactic and therapeutic injections were begun on June 17, and shortly after this there was a decline in

the number of cases and in the number of days lost on account of ivy dermatitis, which continued steadily until the first of August, when the incidence of this condition reached zero. There were no cases in the month of August and only 1 in September, in a man who had not received any injection of ivy extract.

Of the untreated men of the third group, 66 $\frac{2}{3}$  per cent. became affected with ivy dermatitis, whereas among the 2 treated groups of equally exposed men, only 20 per cent. and 7 per cent. respectively were affected.

The percentage of the affected controls corresponds closely with the percentage of adults who have been found by skin test with strong extracts of poison ivy to be sensitive to this plant. It is seen also that protection was established in a greater proportion of the group that received the larger dose than it was in those receiving only one-twelfth that dose.

#### DERMATOPHYTOSIS.—*Treat-*

**ment.**—E. F. Traub and J. A. Tolmach (Arch. Dermat. and Syph. 32:413 (Sept.) 1935) treated 135 cases of dermatophytosis with intradermal injections of **trichophytin**. Apparent cures were obtained in 14 cases, but some of the patients showed early recurrence. Varying degrees of improvement were noted in 58 cases. Many of these patients returned, showing either no further progress or exacerbation of symptoms. In 63 cases no change was observed or the patient's condition was made worse by the treatment. In their experience trichophytin apparently had little if any effect on the course of dermatophytosis. In view of the publicity that this treatment has attained among general physicians, the authors believe that the comparatively small percentage of cases in which definite benefit was obtained hardly warrants

such a tedious and relatively expensive course of treatment in the average case. Two different preparations of trichophytin were used but no difference was noted in the results obtained. Of all the cases for whom a diagnosis of dermatophytosis had been made clinically, 21 per cent. showed a negative reaction to intradermal injections of trichophytin.

The value of injections of trichophytin cannot be accurately determined if effective local treatments are given concomitantly. It is well known that the use of boric acid alone can be of great help in some cases of dermatophytosis. In view of the fact that a patient with dermatophytosis frequently shows periods of remission and relapse, it is felt that the reporting of cures and good results in cases of this disease should be more conservative.

### ECZEMA IN INFANTS.—

**Treatment.**—E. Redaelli (Gior. ital. di Dermat. e sif. 76:765 (June) 1935) obtained favorable results in the treatment of infantile eczema from a diet containing vitamins A and B.

In cases treated with a hypolipoid diet and vitamin B, besides the frequent cure or amelioration of the skin eruption, a beneficial effect on the general condition of the children was noted and they all registered an increased weight. The duration of required treatment was one-third less than in children treated by protein and vaccine therapy.

The author considers the action of the vitamins on the cellular mechanism as nonspecific, with an increase in the oxidation reduction processes and an acceleration of the general metabolism. From the present investigation, vitamin A favorably influences cases of eczema with abundant weeping and vitamin B influences those cases with predominating erythematous and infiltrated lesions.

**ERYSIPELAS.—Treatment.**—Administration of convalescent serum has been advised by E. Neuber in the treatment of erysipelas. It is administered by intragluteal and occasionally by subcutaneous injection. The usual dosage is from 20 to 40 c.c., depending on age, weight and other factors. In the majority of cases 2 administrations are sufficient (from 50 to 80 c.c.), and in mild cases sometimes only 1 is required. The author believes that convalescent serum should have a leading place in treatment of erysipelas. He ascribes the favorable results to the action of specific protective substances present in convalescent serum. Undesirable secondary manifestations, such as shock or delirium, have not been observed.

H. D. Gonzalez and M. Schteingart (Prensa méd. argent. 23:371 (Feb. 5) 1936) used the injection of charcoal in the treatment of erysipelas and state that the entire process follows a rapid evolution to recovery; pain and the sensation of tension of the erysipelas tissues stop, the fever abates and soon after disappears, the erysipelatos patches lose their luster and regress, the general symptoms improve, and desquamation soon and rapidly takes place. The authors inject intravenously an amount that varies between 3 and 5 c.c. of a 2 per cent. suspension of animal charcoal in a 10 per cent. hypertonic dextrose solution. The latter solution prevents the precipitation of the particles of carbon in the suspension and does not modify the therapeutic properties of the drug on erysipelas. The injections prepared with dextrose solution as a vehicle are easily sterilized in the autoclave and can be preserved for a long time without alteration.

### ERYTHEMA INDURATA (BAZIN'S DISEASE).—Treatment.

—L. Glaze (Arch. Dermat. and Syph.

34:888 (Nov. 1936) suggests the use of a mixture of equal parts of **collodion** U. S. P. and flexible collodion U. S. P. in the nonulcerative forms of Bazin's disease.

The affected areas and the sound skin for some distance around it were painted daily for a period of 3 weeks with this mixture. Each new application is made over the previous one. The almost startling results described appeared to have come about as a result of local splinting of the parts from the continuous contractile action exercised by the topical agent.

### **HERPES SIMPLEX. — *Biology.***

O. Naegeli (München. med. Wchnschr. 83:339 (Feb. 28) 1936) states that since 1920 herpes simplex has been regarded as an infectious disease. He admits that, in view of the fact that experimental transmission of the disease is possible, the infectious nature cannot be questioned, since transmissibility of a disease is considered equivalent to causation by a living agent. However, he shows that if the biologic nature of herpes simplex is studied with great care, many factors are discovered that do not tally with the bacterial nature of the disorder. He mentions the influence of puberty, particularly in females; the familial appearance, in which constitutional factors seem to play a part; and, finally, the greater incidence in women. He describes the peculiarities in its appearance and course, pointing out that in the majority of cases herpes appears following some unusual external or internal happening (acute febrile infectious diseases, gastrointestinal disturbances, incretory disturbances, menstruation, trauma, physical exertion or shock). Nevertheless, herpes simplex cannot be compared with the activation of other infectious diseases, for only in some of the cases does the

herpes develop toward the end of the primary disease. Quite often herpes simplex signifies the onset of a disease.

The capriciousness of the onset of herpes simplex is demonstrated particularly in fever therapy with vaccines and in malariotherapy. Occasionally the herpes blisters appear during the first attack of fever, at other times not until the end of the fever therapy, and not at all always following the highest temperatures. Another peculiarity is that the herpes blisters usually reappear at the same sites, so-called virus fixation areas.

Regarding the problem of spontaneous contagion, Naegeli says that the literature reports no unquestionable cases of contact transmission.

Attention is called to the favorable effect exerted by it on other infectious diseases and to the low mortality of pneumonia in patients who develop herpes in the course of the pneumonia and similar observations have been made in meningococcic meningitis, in complicated female gonorrhea, and in malignant diphtheria.

The writer stresses that fever therapy of neurosyphilis is most effective in patients with herpes. Moreover, in some nonherpetic patients with neurosyphilis in whom the first fever therapy has been ineffective he obtained improvement by inoculation with herpes and subsequent activation with fever. Herpetic patients develop neurosyphilis much less often than do patients without herpes. Herpes is more frequent in women than in men, whereas the incidence of tabes and dementia paralytica is comparatively higher in men than in women. Whereas in other disorders the herpes virus seems to influence the disease as such, in the case of syphilis its antagonistic effect involves chiefly the central nervous system.

**HYPERTRICHOSIS.** — *Treatment.*—H. D. Niles (Arch. Dermat. and Syph. 32:580 (Oct.) 1935) treated 12 patients having hypertrichosis with supposedly inhibitory doses of **x-rays to the adrenals**. They received from 1 to 9 treatments, the average number being 3.83. Some patients were given a maximal dose once a month; others, small cumulative doses 3 times a week; and some received both types of treatment. Although with both procedures a few patients showed a slight loss of superfluous hair after the first one or two treatments, this did not continue, and the final result was unsatisfactory in all the treated patients. In spite of these results, the author still believes that hyperactivity of the adrenals may be a factor in some cases of hypertrichosis. Failure may have been due to insufficient dosage or improper intervals between treatments, although several patients received all the radiation that was considered safe. It also may have been due to the fact that in these patients some other gland than the adrenals was at fault. He believes that the ultimate satisfactory treatment of this condition will be from the endocrine point of view.

**LUPUS ERYTHEMATOSUS.**—In 47 cases of disseminated lupus erythematosus observed by P. A. O'Leary, 26 showed clinical evidence of tuberculosis in one form or another. Tuberculosis was demonstrated in 5 of the 10 cases that came to necropsy. The principal changes in the necropsy material were tuberculosis, endocarditis, infarcts in the spleen, diffuse nephritis and terminal bronchopneumonia. Pleural effusion and ascites from passive congestion were noted quite often. Anemia and leukopenia were present in half the cases. Cultures of the blood were positive in 4 instances of 24 cultures made

in 14 cases. Of the 4 positive cultures, 2 were obtained from patients with endocarditis; the third was obtained while the patient was dying. Focal infection was noted in 40 cases. The 20 patients having the acute type died, on the average, 9 months following the dissemination of the disease, whereas 8 of the 27 patients with the subacute type died, on an average, 4½ years following dissemination. Seven patients with the subacute type are cured apparently.

*Treatment.*—In the *subacute type* the treatment advocated by O'Leary consists of **rest in bed, transfusions of small amounts of blood, administration of quinine, plasmochin, small doses of gold sodium thiosulphate and x-ray irradiation of the glandulous regions of the body**. The evidence suggests that disseminated lupus erythematosus is a toxemia in which tuberculosis plays an insignificant part and that evidence of a specific infectious agent, although suggestive, is still lacking.

S. Lomholt (Dermat. Wchnschr. 101: 817 (July 6) 1935) uses the esters of **chaulmoogra and hydnocarpus oil** for the treatment of lupus erythematosus. The drug is given either intravenously in doses of from 1 to 2 c.c. (½ dram) in 9 c.c. (2¼ drams) of an 8 per cent. solution of alcohol or intramuscularly in doses of from 1 to 2 c.c. (¼ to ½ dram) with a proprietary brand of ethyl aminobenzoate, either daily or several times a week. Intravenous injections frequently cause brief periods of headache or dyspnea and occasionally a rise in temperature. An average of 20 injections is given. Of the 31 cases treated, 11 were cured.

**LUPUS VULGARIS.**—*Treatment.*—The results of a new method of treatment by intradermal injection of **phenylethyl hydnocarpate**, employed in 11 cases of lupus vulgaris, are reported

by N. Burgess (Brit. M. J. 2:835 (Nov. 2) 1935). The size of the injection varies according to the size and number of the nodules to be infiltrated. In cases from 1 to 5, the average number of treatments necessary to clear up the affected areas was between 8 and 9. In case 3, "patch 1" was clear, except at one edge, after one treatment, while half of "patch 4" was clear after two treatments. In case 9, the nodules that remained after treatment with ultraviolet rays cleared up after one injection, while in case 11 the lesions in the nasal mucosa cleared up after 6 injections. Cases 6, 7, 8, and 10 are still under treatment. In case 6, treatment was somewhat irregular, and on one occasion there was a rather severe local reaction. A similar reaction, but more intense, was observed in case 9, in which only one injection was given. In case 9, no lupus nodules were visible when the reaction had subsided. In the remaining cases the induration was relieved in a few days. Less improvement has been noted in case 6 than in the other instances. Case 10 is of interest in view of Muende's failure to obtain good results in children with creosoted moogrol. This case has only just come under treatment, but the reaction following the first injection is comparable with that seen in adults. Cases 5 and 11 show the value of the treatment affecting the mucous membranes. The cases still under treatment are making satisfactory progress.

The advantages of this method of treatment are that (1) comparatively little pain is experienced by the patient; (2) the treatment sessions are of short duration; (3) the technic of treatment is simple; and (4) after treatment very little scarring is present, the skin being quite supple. The results so far obtained indicate that the method is worthy of a more extensive trial.

E. Scolari (Gior. ital. di Dermat. e sif. 76:665 (June) 1935) found that although Sauerbruch-Hermannsdorfer-Gerson diet influenced the majority of cases of lupus favorably, in no single case was a complete definite cure obtained by the diet alone. In the early stages of the treatment an increased circulatory activity was observed in the diseased areas. By the capillaroscope and by electrothermometry it was found that there was both an increased quantity of blood passing through the vessels and an actual new formation of vessels. In the Milan Clinique cases treated by the diet seldom did badly. In one case a quiescent lung lesion again became active, and in another a lymphatic spread occurred. No cases of tubercles, necrosis of foci or general miliary tuberculosis were seen as have been reported in other clinics. Cases treated with gold injections or tuberculin simultaneously with the diet improved more quickly than those treated by the diet alone. Finsen light treatment and chemical caustics were found very helpful in the later stages in healing isolated nodules. For comparison, nontuberculous conditions were also treated with the diet. The best results were obtained in conditions associated with edema and sweating, such as in the erythrodermias. Incomplete or negative results were obtained in psoriasis and lichen. Lupus erythematosus was helped by the diet treatment. The mechanism of the action of the diet is still obscure. The author believes that the good results are due to an increase of the defense mechanism due to a focal reaction in the lesion. Cases which give a marked tuberculin reaction do best on the diet. There were also signs of an increased activity of the reticulo-endothelial system when the diet was given, and it is suggested that vitamins may play a part in the results.



**PELLAGRA.**—Basing their work on the existence of an intrinsic deficiency in pellagra, V. P. Sydenstricker, E. S. Armstrong, C. J. Derrick and P. S. Kemp (*Am. J. M. Sci.* 192:1 (July) 1936), in imitation of the investigation of Castle and his associates on pernicious anemia, tried the efficacy of normal gastric juice in the treatment of pellagra in typically advanced cases. Recent alcoholism and obstructive lesions of the gastrointestinal tract were absent. Gastric juice was obtained from normal medical students and from patients with no gastrointestinal disease. To obviate the probability of increased gastric digestion of food, all doses of gastric juice were administered 4 hours after the evening meal.

Six cases of pellagra were treated with gastric juice in varying amounts given over periods of 10 to 49 days. In one instance, ground raw beef was incubated with the gastric juice and the predigested beef administered daily for 10 days. Three cases of severe pellagra improved more rapidly than experience would have led the investigators to expect even when optimum diet fortified with vitamin B<sub>2</sub> is administered. One case of moderately severe pellagra improved rapidly and was in complete remission after 23 days. One case of extremely severe febrile comatose pellagra survived for 51 days with the administration of gastric juice. All patients except one were fed a pellagra-producing diet.

The results obtained by administration of gastric juice to a small number of pellagrins maintained on pellagra-producing diet would indicate that unusually rapid recovery may take place under this treatment.

**PEMPHIGUS.**—*Etiology.*—In an attempt to prove the identity of these dermatoses with the group of diseases

caused by an invisible virus, E. Urbach and S. Wolfram, of Vienna (*Arch. Dermat. and Syph.* 33:788 (May) 1936), obtained material from 34 patients with pemphigus and dermatitis herpetiformis. Animals inoculated subdurally with blister fluid exhibited signs of the disease in 91.8 per cent. of cases of pemphigus, 100 per cent. of cases of localized pemphigus, and 70 per cent. of cases of dermatitis herpetiformis. The histologic changes registered in the brain substance of the experimentally infected rabbits were always those of meningoencephalomyelitis. Animals inoculated with virus from patients with pemphigus showed the same symptoms as those into which material from patients with dermatitis herpetiformis had been introduced. Just as the course of dermatitis herpetiformis is milder in human beings, so in animals it is characterized by lesser morbidity and mortality. The symptoms point unreservedly to one and the same pathogenic agent as responsible for both pemphigus and dermatitis herpetiformis. The symptoms and histologic changes observed in passage animals correspond exactly to those occurring in animals infected directly with human virus. Since microscopic and cultural studies gave invariably negative results, it must be assumed that an invisible virus, necessarily filterable, is being dealt with because the transfer of the infection from the human being to animals and its further passage through animals was successful with filtered material.

The involvement of the central nervous system was marked in all animals infected with material obtained from patients with pemphigus in the florid stage. The picture composed by the symptoms and the histologic changes in the central nervous system closely resembles that produced in animals by the virus of herpes. Attempts to secure

crossed immunity between pemphigus and herpes failed, while animals which recovered from an attack of pemphigus usually displayed an immunity to reinfection with pemphigus. The supposition that pemphigus is caused by a virus is further strengthened by the results of inoculations of animals with material obtained from the two patients at necropsy. Passage through animals was successful in both cases; the material used consisted of filtrates of normal and diseased skin, spleen and lymph nodes. By serologic tests it was possible to demonstrate that the disease manifested by the experimental animals was the same as pemphigus in human beings.

**PSORIASIS.—Pathogenesis and Treatment.**—It is believed by O. Grutz that psoriasis is caused by a disturbance in the fat metabolism and that it can be counteracted by a diet deficient in fat. The following foods should be avoided: bacon, lard, butter, cream, oil, pork, mutton, goose, duck, herring, salmon, carp, fish roe, egg yolks. Cakes and other baked foods containing fats must likewise be avoided. Permitted are lean meats, fish with a low fat content, soups and vegetables, provided they have been prepared without fat, fruits and berries, preserves, fruit juices, and various breads that have been prepared without fat. On such a diet, obese patients with psoriasis frequently lose weight, while patients of normal weight do not, provided their calorie requirements are adequately supplied in the form of carbohydrates and proteins. Emaciated persons with psoriasis have even been known to gain in weight under the influence of the fat deficient diet.

The author discusses the possibility that just as the carbohydrate tolerance differs in diabetic patients, there may be a difference in the fat tolerance of psoriatic patients. On the basis of clini-

cal manifestations this seems probable, for in some patients a slight reduction in the fat intake is effective, while in others a more strict regimen is necessary. Moreover, it is advisable to investigate whether the fat synthesis is disturbed in psoriatic patients. The author reports that in some patients the results of the **fat-deficient diet** are noticeable after 2 or 3 weeks, while in others 6 weeks or even several months are necessary to reveal the effects. In some patients the psoriatic lesions spread in area but decrease in depth shortly after the onset of the treatment, and there may also be a temporary increase in scaling; this should not, however, tempt the physician to interrupt the treatment, for this "becoming acute" is only temporary and the continuation of the diet will finally effect the complete disappearance of the lesions.

**Liver therapy** is favorably regarded by T. Grüneberg. Injections of liver extract are given every second day, and the patient takes liver by mouth in the form of either fresh liver or liver extract. In psoriatic patients, liver therapy decreases the tendency to relapse, but it also influences the existing cutaneous manifestations. It appears that a better therapeutic effect is obtained if the patient is exposed to the influence of **light**, but the exposure should not be too severe. In order to compensate for the deficiency of sunlight in the big city, particularly during the winter months, the patients were given **quartz lamp irradiations**; the doses were smaller, however, than is usually the case, in order to avoid irritation.

In spite of the fact that the liver therapy occasionally produces surprisingly good results, the author admits that, aside from a reduction in the tendency to relapse, it accomplishes, on the whole, no more than the usual methods of treatment; for liver therapy

may fail as well as the other treatments, and, as a rule, it does not make the application of ointments unnecessary. The mechanism of liver action, which may involve several components, is not yet clear, but it is possible that an increase in the sulphur or glutathione content of the skin is an essential factor.

J. Grüneberg (München. med. Wchnschr. 83:561 (Apr. 3) 1936) gives subcutaneous or intramuscular injections of from 2 to 6 c.c. ( $\frac{1}{2}$  to  $1\frac{1}{2}$  drams) of **adrenal cortex** every day or every second day in the treatment of psoriasis. The dosage is determined by the severity of the case, and the duration of the treatment by the rapidity with which the results become manifest. As a rule, it is necessary to continue the treatment for at least 5 or 6 weeks. Some improvement is usually noticeable long before this time. The administration of the cortical extract is frequently inadequate for a complete cure and it is combined with local measures. The treatment is most effective in the form of psoriasis that is complicated by arthritic processes. The author believes that it should always be tried in these cases. Generalized psoriasis, likewise, responds favorably to the adrenal cortex treatment. Relapses are not prevented, however, by this therapy, although prolonged treatment may have a certain after-effect, particularly in the complicating articular processes.

W. Lutz (Schweiz. med. Wchnschr. 65:1169 (Dec. 7) 1935) believes that psoriasis is a metabolic problem. He reports 3 cases of psoriasis vulgaris in which he obtained favorable results with the oral administration of **cevitamic acid**.

The acid was given in the form of tablets, each containing 0.05 Gms. ( $\frac{3}{4}$  grain), and in the form of powders, each containing 0.25 Gms. (4 grains)

of cevitamic acid. The dose—1 to 3 tablets 4 times daily.

The cases responded favorably to treatment; the results, however, were not lasting and the author believes further therapeutic trials are justified.

**SCABIES.—Treatment.**—Attention is directed by G. V. Kulchar and W. M. Meininger (Arch. Dermat. and Syph. 34:195 (Aug.) 1936) to a recent report by Ravaut and Mahieu, in which those authors described the successful treatment of scabies by the precipitation of colloidal sulphur on the skin through the interaction of sodium thiosulphate and an acid. The treatment is carried out as follows: The patient is directed to take a soap and water bath. After he is thoroughly dry, a 40 per cent. aqueous solution of **sodium thio-sulphate** is applied over the entire body, except the head and face; particular attention is paid to the areas between the fingers, to the flexural surfaces of the wrists, and to the breasts, abdomen, buttocks, thighs, and external genitalia. Fifteen minutes later 4 per cent **hydrochloric acid** is applied in a similar way, and 1 hour later the applications are repeated in the same order. The procedure is repeated the next day; on the following day the patient again bathes and changes to fresh clothing. All bed linen, sleeping garments and clothing previously used are sterilized by boiling for 5 minutes.

As the solutions are stable, they may be made up in large quantities and dispensed as needed. Four ounces (120 c.c.) of each solution is sufficient to carry out the treatment.

The authors used sodium thiosulphate in treating 50 patients with scabetic infestations of all degrees of severity. As a control, 50 patients were treated with an ointment prepared in the manner described by Greenwood. The conclu-

sion was reached that the precipitation of colloidal sulphur on the skin by the interaction of a 40 per cent. aqueous solution of sodium thiosulphate and a 4 per cent. solution of hydrochloric acid provides a simple, effective and economical method of treating scabetic infestations.

### SCLERODERMA.—*Treatment.*

—Believing that a relationship exists between scleroderma and the different endocrine glands, E. L. Oliver and J. Lerman (Arch. Dermat. and Syph. 34:469 (Sept.) 1936) treated a series of cases of scleroderma with daily injections of posterior pituitary. In most instances an ampoule of 1 c.c. (16 minims) of solution of posterior pituitary was given. The injections were continued for from a few weeks to a month at a time, followed by an interval of a month or more without treatment. Some of the patients were started on daily injections of 1 c.c. of **pancreatic extract** for a month as a control series. The clinical histories of 3 cases are reported, 1 each of the morphea, linear band, and diffuse types. They summarize their observations as follows: Twenty patients with scleroderma of different types were treated with daily injections of solution of posterior pituitary. In 3 cases of *morphea*, some or all of the lesions disappeared completely, leaving slight pigmentation. In the others, varying degrees of improvement were observed. In 2 cases of the *band-like type* improvement was marked. In a case in which the condition was associated with a severe degree of hemiatrophy of the face, improvement at first was considerable, but no further improvement was noted after the first few months. Naturally, the atrophy was unchanged. In 5 cases of *sclerodactylia* associated with *diffuse scleroderma* of the face and neck, marked

improvement was noted in the face and neck, the skin becoming definitely softer. In the other 3 cases of a similar condition, some improvement was noted. This improvement was manifested in several instances by ability to wrinkle the forehead and disappearance of the mask-like expression characteristic of this condition. In one of these cases the skin of the neck became normal in appearance except for pigmentation. In 3 cases of *sclerodactylia* marked softening was noted in the skin of the hands as well as increased mobility and relief from pain. In 2 cases the improvement was so slight that treatment was discontinued.

**SEBACEOUS CYST.**—S. Feldman (Arch. Dermat. and Syph. 34:492 (Sept.) 1936) reports a treatment for sebaceous cysts which has yielded uniformly good results in the last 5 years, with less scar formation than usually results from surgical treatment.

In dealing with an infected sebaceous cyst a large 18-gauge needle attached to a syringe is inserted into the cavity of the cyst at its most dependent position, and the **pus is aspirated**. Sometimes it is necessary to withdraw the needle and express the contents of the cyst through the opening. After this, a needle attached to a syringe containing 95 per cent. alcohol is reinserted through the same puncture hole and enough **alcohol is injected** into the cavity of the cyst to produce slight tension, with blanching of the skin. This causes a mild burning sensation, which wears off in a few minutes. The needle is then withdrawn and the fluid is again removed by means of gentle pressure. This process may be repeated several times, until practically a clean fluid returns. A **drain** made of several strands of horsehair or of chromic catgut is inserted into the opening and a dressing is applied. This is allowed

to remain for about 3 days. The drain is then removed, the cavity emptied, and alcohol is again injected.

In the case of a small cyst, when the dressing is removed after a few days, the drain will usually be found on the dressing and the cavity will be practically or entirely closed. For a larger cyst, the process may have to be repeated several times until the desired result is obtained. Occasionally the entire capsule of the cyst will present itself at the opening and will lend itself to removal through the opening by means of forceps; or the opening may have to be slightly enlarged if the capsule happens to be thick and hard. The result, however, is uniformly good and the scar is hardly preceptible.

When the cyst is not infected and the contents are firm, alcohol is injected into the cavity of the cyst under sufficient pressure to produce a mild blanching of the overlying skin, and the needle is withdrawn, allowing the alcohol to remain. The slight pain which results wears off in a few minutes. The result of this treatment is that the firm material within the cavity of the cyst becomes softened sufficiently after a few days so that it can be expressed through the opening. A small cyst may become sclerosed after one injection. In larger cysts another and even a third injection may be needed to liquefy the contents of the cyst sufficiently to permit of its removal through the needle puncture. After this procedure, the lesion is treated in the same manner as an infected cyst.

Pus cavities in cases of acne conglobata have been treated by this method, and while it was possible to effect healing, scarring could not always be avoided.

#### SKIN DISEASE.—*Treatment.*—

E. Davis (Brit. J. Dermat. 48:491 (Oct.) 1936) suggests that charcoal should be used intravenously only on

those selected cases which have previously proved resistant to all forms of therapy or were obviously doing badly on the usual treatment.

Charcoals of different absorptive powers have been studied, wood charcoals compared with animal charcoals, and the influence of the fluid in which the charcoal was suspended has been assessed. The average size of the particles of the charcoals used was 1-4. The charcoal was made up in fresh 2 per cent. sterile suspensions in distilled water, saline or gum-saline.

Some preliminary animal experiments were carried out in conjunction with S. L. Prescott in Prof. Macdonald's laboratory at Manchester University. It was found that charcoal could be given intravenously without harm to cats, in doses (per kilo.) much greater than those contemplated clinically. Charcoal was then cautiously injected to convalescent and healthy subjects (including the author), without ill effect. Subsequently, more than 800 intravenous injections were given to 330 patients.

No essential difference was noticed between wood and animal charcoals. Charcoal intravenously acted in much the same way on all afebrile individuals, whether they were diseased, convalescent or healthy. In general, the effect of charcoal suspended in gum-saline and injected in doses of 4.0 to 5.0 c.c (1 to 1¼ drams) into afebrile subjects was to cause a rise in temperature, pulse and respiration, beginning in 3 hours, reaching a maximum about the fifth hour, and subsiding at the eighth hour. The average increase in temperature was 3° F., and in pulse and respiration 25 per cent. In addition, subjective reactions of varying degree, from mild to severe, usually accompanied the temperature, pulse and respiratory change. Summing the symptoms of all the patients, there were noted headache,

dizziness, malaise, nausea, backache, pain in the chest and limbs, chills and rigors; and infrequently, sore throat, coryza and herpes. Occasionally there was no subjective response or temperature, pulse and respiratory response, or no apparent response whatever.

It must be pointed out that whereas charcoal in gum-saline produced the above general response in 90 per cent. of cases, charcoal in distilled water or saline gave the response in only 30 per cent. of cases, and further, any response was usually feeble. Control injections of gum-saline gave rise to no reaction.

A certain minimum dose of charcoal, usually about 4.0 c.c. (1 dram), must be given to produce the general response described. Smaller doses gave rise to feeble effects, or no apparent effect. The same dose of charcoal, repeated at intervals of 24 to 48 hours, tends to evoke a diminished reaction. The effect of the first injection could often be maintained or exceeded by increasing subsequent doses by 0.5 c.c. (8 minims).

In 6 cases out of 330, intravenous charcoal, either animal or wood, was followed by immediate collapse and a shock-like reaction. Within 2 minutes of injection the patient showed cyanosis, dyspnea, coma, prostration, vomiting, feeble pulse and incontinence. Recovery began in each case within 5 minutes, and was complete in 12 hours. Collapse occurred only in very feeble patients or with high doses of charcoal. One of these patients was an asthmatic.

The dosage of charcoal recommended is as follows: For an adult, treatment should begin with 4.0 c.c. (1 dram) of a 2 per cent. suspension in distilled water or gum-saline. (Children tolerate charcoal well in doses of 2 to 3 c.c.— $\frac{1}{2}$  to  $\frac{3}{4}$  dram). Each successive dose should be increased by 0.5 c.c. (8 minims) and given at intervals of 24 to 48 hours. Charcoal should be continued until re-

covery seems established, and repeated, should there be signs of a relapse, or if recovery becomes sluggish. Charcoal is contraindicated in very debilitated patients. A collapse reaction contraindicates further charcoal, and doses of 8.0 c.c. (2 drams) or more should be given with caution if at all. Charcoal injections should preferably be given with the patient in bed, although they have been given without ill-effect in selected ambulatory patients. It is advisable to lubricate the syringe and needle with vaseline or glycerin to ensure ease of injection of the charcoal. If 4 injections have been given without benefit, it is unlikely that charcoal will be of use.

*Summary.*—1. The effects of charcoal, administered intravenously, have been studied. Over 800 injections have been given to 330 patients.

2. Intravenous charcoal injections given to afebrile individuals often caused an elevation of pulse, temperature and respiration, which may be associated with chills and rigors.

3. Fifty severe skin cases were treated with intravenous charcoal injections, and the results suggest that charcoal is worthy of trial in the therapy of skin diseases.

**SNAKE BITE.**—*Treatment.*—In a paper read before the Scientific Meeting of the Allegheny County Medical Society of Pennsylvania, by A. Atkinson (Pittsburgh Med. Bull. 25:493 (June 6) 1936) he stated that there are 3 species of poisonous snakes in the natural fauna of Western Pennsylvania.

Our native species in the order of their numerical occurrence are: the copperhead; the banded or mountain rattlesnake; and the swamp rattlesnake. They all belong to the pit-viper group, which is characterized by a prominent pit or blind opening between the eye and the

nostril, and two long, curved, hollow teeth on the superior maxillary bone that are capable of being erected when the mouth is opened widely. These teeth are connected with the poison glands by a closed duct, and when the snake strikes, the poison is forced through the canal of the hollow tooth by the contraction of the muscle. The poison is expelled at the point of deepest penetration of the tooth, an important point in the treatment of these wounds.

The mortality of snake bite in Pennsylvania is about 3 per cent.

The treatment of snake bite is essentially that of any poisoned wound: **free incision, evacuation of poison, and drainage**, with special consideration of the physiological action of the poison concerned.

In the pit-vipers there are 2 distinct poisons in the venom. (1) The neurotoxic element is present in only small amounts in this class of snakes; it acts on the central nervous system, and if present in sufficient amount will cause death by respiratory failure. (2) The hemorrhagic element, which predominates in this group, attacks the vessel walls and allows the escape of red corpuscles into the tissues near the point of the wound, and later on in various parts of the body. This hemorrhagic element, by destroying the walls of the small vessels, keeps the poison from being carried away by the blood stream unless, as rarely happens, the fangs penetrate a large vessel.

The toxic elements are moved from the site of the bite through the lymph channels. This permits of successfully treating these wounds by multiple puncture and various forms of suction.

Each time the snake strikes the victim directly it will leave 2 punctured wounds  $\frac{1}{2}$  to 1 inch apart, depending on the size of the snake. If he strikes obliquely or if one fang is broken off, there may

be only 1 wound. These wounds are easily seen, bleed slightly, and after a few minutes are surrounded by an inflamed area. A **band** should be applied at a convenient point between the wound and the heart (usually the knee or elbow) tightly enough to shut off the superficial venous circulation, but not the arterial circulation. The surface of the limb should be washed with **alcohol** or other antiseptic. A cruciform incision should be made through each of the wounds, cutting  $\frac{3}{4}$  inch long and  $\frac{1}{2}$  inch deep. This should always be made deep enough, as the poison lies at the bottom of the wound, and it is an easy matter to take care of the wound after getting rid of the poison. With the tourniquet in position, such a wound will bleed freely, and often the amber-colored poison may be seen to come out when the cut is made. This bleeding should be encouraged by **suction**, using one of the commercial suction cups if at hand. If not, suction by the lips may be used, which is a very efficient method. There is no reason to fear that the poison will get into carious teeth or slight mouth abrasions, and any small amount swallowed will promptly be destroyed by the gastric fluid.

This should be done at the earliest minute possible, but even if the patient is not seen until as much as 24 hours has elapsed, it should be done thoroughly. The more venom extracted in this manner, the better the results obtained. In 20 minutes the band is removed and replaced lightly about 5 or 6 inches above the wound, just tightly enough to obstruct lymphatic flow and not blood circulation, as in the group of snakes being dealt with the poison is spread by the lymphatics. A ring of **incisions** should be made around the wounds about 2 inches from the fang marks; these incisions should be  $\frac{1}{4}$  inch deep, 1 inch apart; if not seen before inflammatory

swelling has occurred another series of cuts should be made at the edge of the swollen area. Plenty of cuts for extraction of poison should be made; in severe cases 50 to 100 incisions are none too many.

Suction cups should be used on the cuts for 20 minutes of each hour. When the suction cups are not in position, the region of the wounds should be kept covered by a **hot boric acid** or **hot magnesium sulphate pack** to promote drainage, leaving the lightly applied band in position all the time. This should be kept up in all cases for 24 hours and in severe cases until recovery or death.

If **antivenin (cortalus neoartica)** is available, not less than 4 syringes of 10 c.c. each should be given by multiple injections around the wounds and at numerous points throughout the swollen area. Less than 40 c.c. are of little benefit and in bites of the large western and southern species, 60 to 100 c.c. should be used. Antivenin should not be used during the first 2 hours, and after using it suction should be discontinued for a period of 2 hours. If the victim becomes toxic at any time, **blood transfusion** of suitably typed blood may be given and also 1,000 c.c. (1 quart) of 10 per cent. **glucose solution** at 6-hour intervals.

Snake bite is always an emergency and must be treated as such, and the best must be made of such equipment as may be at hand. Too much attention need not be given to the knife; any sharp knife will do—scalpel, razor blade, or pocket knife. A handkerchief, rope, twine, or strips of clothing will do for a tourniquet. Use an antiseptic solution if at hand, but if none is available, cut at once; the motto in the field is "get that poison out." After a house or hospital is reached, the aseptic technic may be used and any infection overcome

that may have occurred in the field. In 2 cases treated during the past year, the writer used **leeches** instead of suction cups, and they served the purpose very well.

The injection of any substance into the tissues around the bite (except antivenin) is not justified by present knowledge. Potassium permanganate, phenol, formaldehyde, and picric acid solutions used in this manner do no good and increase the danger of necrosis and gangrene.

**SPIDER BITE (ARACHNIDISM).**—*Diagnosis.*—G. Walsh and A. S. Hargis (South. Med. and Surg. 97: 673 (Dec.) 1935) report a series of 12 cases of spider bite observed during the past two years.

Professional interest has directed itself in two ways: (1) in an attempt to discover an adequate form of treatment, which would relieve the terrific pain and the mental anxiety and prostration following the accident; and, (2) what is probably more important, to learn the symptoms following a spider bite in their variety of forms, so that patients who have suffered from this type of injury will not be subjected to needless surgery.

Surgical procedures on patients suffering from spider bites are fairly common in sections of the country where this accident is of frequent occurrence. One case has been reported in which laparotomy was performed because the physician could not believe that the symptoms from which the patient was suffering could have resulted from a spider's bite. This type of mistake will occur until the profession has been thoroughly informed concerning the subjective and objective symptoms which the bite of a spider produces.

The history of these cases may be of the utmost value or it may be valueless and misleading. There should be very



little difficulty in the diagnosis, with the history of genital bite, particularly while using an outdoor toilet. Of the 29 cases previously reported, 20 were bitten on the genitalia.

A bite from this insect produces not only intense and lasting pain, but also, in some cases, a mental condition similar to that induced by certain drugs, a marked impairment of the patient's knowledge of time and place, and of his judgment as to his requirements and needs. The pain is so intense that the individual is concerned only with something that will mitigate his suffering. The physician must, therefore, be prepared to diagnose cases of arachnidism without any history at all. Genital bites are received most frequently early in the morning, when the patient first visits the outdoor toilet. However, several of the reported cases were bitten just after dark in the same manner. Children at play are more apt to receive their bites during daylight hours.

On several occasions the writers observed a certain rhythm in the pain which comes and goes with a stated periodicity. The patient will cry out, twist and turn violently on the bed, and then will relax temporarily, with periods of comparative comfort. This periodicity may be so marked as to suggest major hysteria. The pain may be widely disseminated; it may occur not only in the abdomen, but also in the thighs and chest. This wide distribution of pain is of first assistance in ruling out perforated gastric or duodenal ulcers. It should be remembered, however, that abdominal rigidity may be first to develop, and may be the only rigidity present when the patient is first seen. Search for rigidity in the lumbar muscles and the thigh muscles is most helpful in solving the problem of a presumed spider bite.

The suddenness with which the symptoms appear in an individual who has been in perfect health is an aid in arriving at a correct diagnosis.

*Treatment.*—In a number of instances the intravenous medication of glucose has given quick and permanent relief. The intravenous use of magnesium sulphate has also been satisfactorily reported. The use of a hot tub-bath frequently repeated, is one of the most helpful procedures in the treatment of spider bites. Morphine and the barbiturates are necessary to control the pain.

**VERRUCA.**—*Treatment.*—A 1.5 per cent. solution of bismuth sodium tartrate has been used by H. Shellow in the treatment of 97 lesions of various types of verruca occurring in 73 patients. The skin about the lesion is prepared by washing with soap and water; iodine and alcohol are then applied. A fine hypodermic needle is used to pierce the skin just outside the zone of hyperkeratosis and directed downward and inward toward the base of the verruca at the most active point, the end of the needle remaining just above the corium. From  $\frac{1}{2}$  to 2 minims (0.03 to 0.12 c.c.) of bismuth sodium tartrate solution is injected, according to the size of the lesion. In from 1 to 3 days after the injection a dark hemorrhagic area appears, visible through the keratotic surface. This denotes that the drug has taken effect. In the markedly keratotic hard type of ordinary verruca vulgaris, this phenomenon may not always be seen. In most cases, from 1 to 3 days after the first injection there has been either a complete cessation or a marked diminution of pain. The peripheral redness that so often accompanies the painful verruca disappears in from 2 to 7 days. All papillomatous lesions flatten

out decidedly after the first injection, and in the plantar or palmar types, the surface becomes smoother. If within 7 to 14 days following the appearance of the hemorrhagic center, the top of the verruca has not come off or the central portion has not fallen out, the keratotic tissue may be removed to determine whether any activity is still present. In most instances, after a lapse of from 14 to 17 days following the initial injection, the removal of this hemorrhagic keratotic center reveals an underlying normal appearing epidermis. If after 2 weeks of further observation an active verrucous tissue is seen, the lesion may be reinjected. Of the 97 lesions, most of which had been treated previously by other measures, 89 were cured, 5 improved, and 3 showed no improvement.

In 67 cases the lesions were of the painful palmar or plantar variety, and 18 were of the verruca vulgaris type occurring on the dorsum of the hands or feet.

**VITILIGO.**—A 10 per cent. alcoholic solution of oil of bergamot is recommended by M. H. Cohen in the treatment of vitiligo. The affected areas are treated twice a week. The lesions are painted with the oil of bergamot solution and then followed by use of the **ultra-violet radiation** for a period of from 3 to 5 minutes. An intravenous injection of **gold sodium thiosulphate** (0.1 Gm. -  $1\frac{1}{2}$  grains) is given once a week.

Improvement is seen to occur within 2 weeks and in 6 weeks many lesions will have entirely disappeared.

## RADIOLOGY

By ROBERT SHOEMAKER, 3RD, M.D.

**X-RAYS.—X-RAY DIAGNOSIS.—X-ray Pelvimetry and Fetal Cephalometry.**—R. P. Ball (Surg. Gynec. and Obst. 62:798 (May) 1936) gives in detail his technic for determining from 2 x-ray films of the pelvis of a pregnant woman the volume of the fetal

able increase predicted by use of the graph (Fig. 1). In case of marked disproportion of head and birth canal a second x-ray examination may be desirable to ascertain if volumetric increase of head is beyond normal limits. In cases in which the fetal head volume was 150

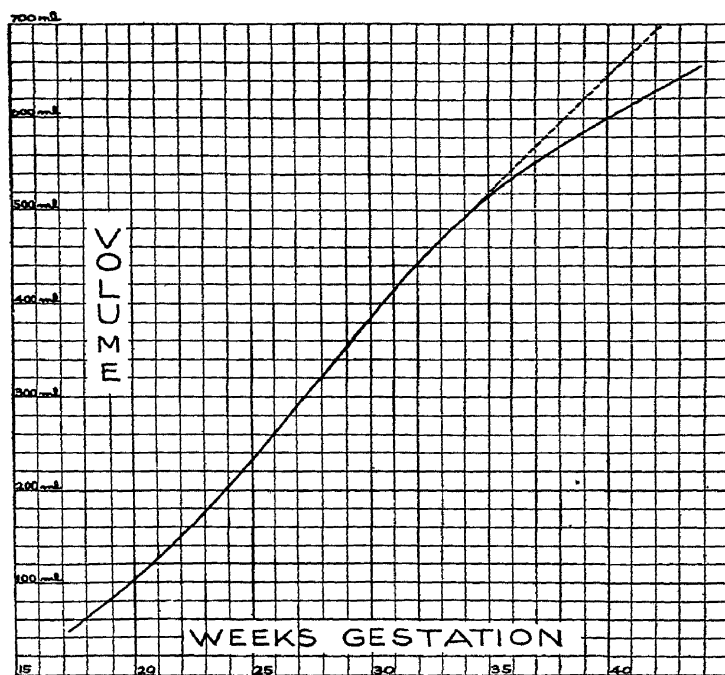


Fig. 1 —Graph showing absolute rate of increase in volume of fetal head *in utero*. (Ball: Surg. Gynec. and Obst.)

head and the volume of a sphere which will just pass through the smallest diameter of the birth canal. The difference between these two volumes is a measure of the amount of molding of the fetal head which will be required during delivery. If the volume of the fetal head is determined 10 weeks before term, it may be compared with the normal size of the fetal head at this period and its prob-

milliliters more than the volume of a sphere which would just pass through the true conjugate diameter, there has been a fetal mortality rate of 80 per cent. during spontaneous labor.

The author has classified the pelvis which he has measured from x-ray films in 3 types according to the ratio—TRUE CONJUGATE DIAMETER, BISHOP'S SPINE DIAMETER.

TABLE I

*Incidence of Type Pelves Classified According to the Pelvis Index—See Fig. 2*

| Type of pelvis            | White |                     | Negro |                     | Total | Total               |
|---------------------------|-------|---------------------|-------|---------------------|-------|---------------------|
|                           | Cases | Incidence per cent. | Cases | Incidence per cent. | Cases | Incidence per cent. |
| Index one plus . . . . .  | 56    | 40                  | 14    | 22                  | 70    | 35                  |
| Index one minus . . . . . | 32    | 20                  | 18    | 30                  | 50    | 25                  |
| Index one . . . . .       | 50    | 40                  | 30    | 48                  | 80    | 40                  |
| Total . . . . .           | 138   |                     | 62    |                     | 200   |                     |

Type I, the true conjugate diameter is greater than the biischial spine diameter so the ratio is greater than I. The author calls this Index I plus.

Type II, the true conjugate diameter is less than the biischial spine diameter so the ratio is less than I. This is called Index I minus.

Type III, the true conjugate diameter is equal to the biischial spine diameter so the ratio is equal to I. This is called Index I.

TABLE I shows the incidence of these three types of pelves in a series of 200 white and negro women which he measured by his method of x-ray pelvimetry. The 3 types of pelves are shown graphically in Fig. 2.

The two x-ray films which the author uses for making his measurements are a true anteroposterior with the patient supine upon the table and the anode of the

tube exactly 30 inches from the film, and a true lateral position with the patient lying on her right side on the table with the anode-film distance 30 inches. In cases of presentation other than cephalic, 2 additional films are required, with the central ray passing directly through the fetal head, and the woman in the same positions as above.

The volume of the fetal head is determined by measuring the circumference of the shadow of the fetal head on both the A. P. and the lateral films. The author had devised a clever modification of a map-measurer or planimeter for this purpose. This is shown in Figs. 3 and 4 and has been named the *pelvicephalometer*.

The use of the pelvicephalometer is described by the author as follows: "When an x-ray exposure is made the roentgenographic image naturally shows

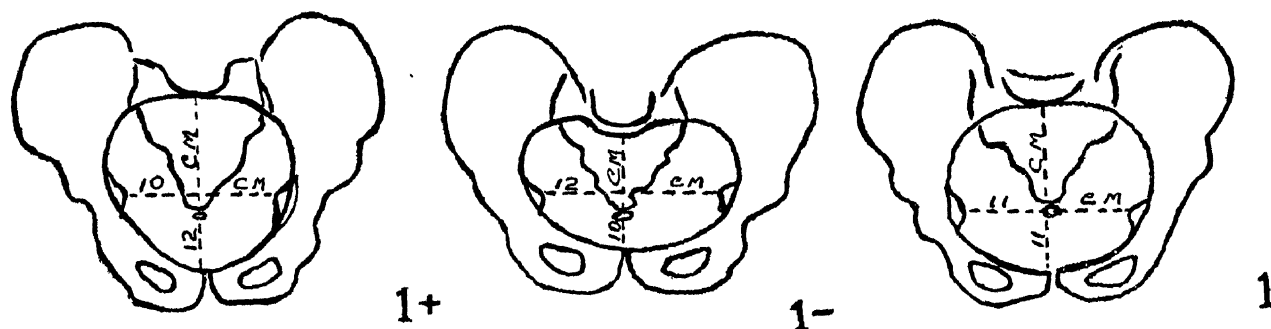


Fig. 2.—Schematic drawing of types of pelves classified by measuring true conjugate and biischial spine diameters. (Ball: Surg. Gynec. and Obst.)

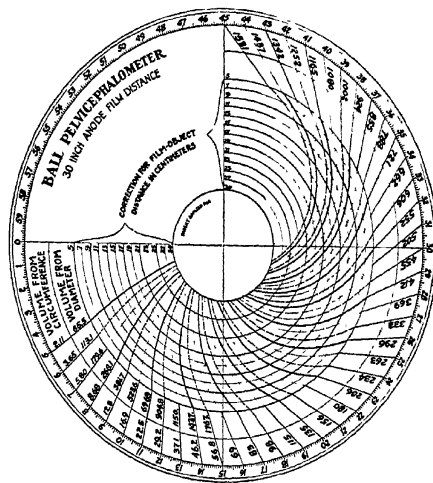


Fig. 3.—Calculator for correcting roentgenographic magnification without mathematical calculation (Ball, Surg, Gynec and Obst.)

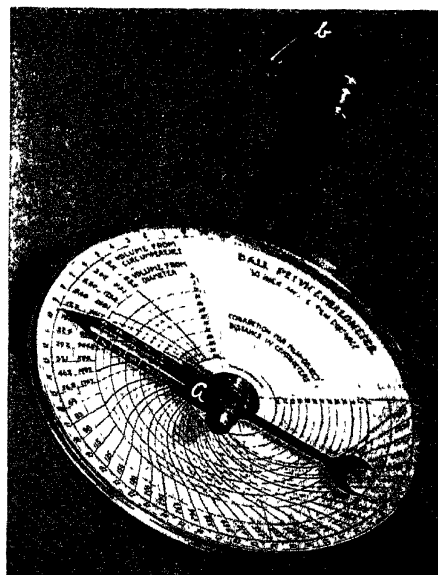


Fig. 4.—The pelvicephalometer. (Ball, Surg, Gynec. and Obst.)

a certain degree of enlargement, depending upon the distances of the object from the film and from the anode. In the diagram, Fig. 5,  $X$  represents the anode;  $AB$ , the object;  $CD$  the film;  $XZ$  the anode film distance; and  $XY$  the anode object distance.

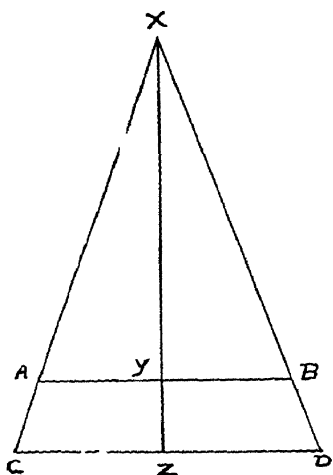


Fig. 5.  
(Ball. Surg., Gynec. and Obst.)

The object  $AB$  will be registered upon the film as size  $CD$  if the object film distance is  $YZ$  and the anode film distance is  $XZ$ ; or  $CD:AB::XZ:XY$ .

If one of the three variable factors— anode film distance,  $XZ$ —is made constant, a correction chart for the other two  $YZ$  and  $CD$  can be plotted with rectangular or polar coordinates (Fig. 3).

In this method, a 30-inch anode film distance is arbitrarily selected and the two other variables are corrected by means of the pelvicephalometer (Fig. 4). This instrument consists of a calculator (dial) to which is attached a pointer,  $A$ , connected to the rotor  $B$ , by a shaft and a gear so that the pointer always indicates the distance traveled by the rotor.

The calculator (Fig. 3) is a circular rule obtained by the plotting of polar coordinates, the points being located arbitrarily. There are 60 cm. divisions on the perimeter of the calculator, and the subjacent radial curved lines are

intersected by concentric circles which represent the *object film* distances in centimeters.

The 2 tables on the calculator represent in milliliters the volume of a sphere of a known circumference or diameter. These tables are used to compare the volume of the fetal head with the volume capacity of a pelvic diameter. By this means the passenger to passage ratio can be expressed in similar units, and the amount of molding necessary for the head to pass through the pelvic diameter can be better visualized.

When the roentgenographic image is measured and the object film distance is known, the pointer is retraced, by manipulating the rotor with the finger over the radial line subjacent to the centimeter size until it rests over the point of intersection of the concentric circle and the subjacent line.

Figures corresponding to the concentric circles appear on the pointer, for convenience in locating the point of intersection. After the pointer is placed at the intersection, the corrected size is read from the figure in the outer row over which rests the tip of the pointer. Hence, by the use of this instrument, a linear or spheroid roentgenographic image can be measured and its magnification corrected simply by shifting the pointer of the pelvicephalometer. The determination of the object film distance is described in the method of computation.

*Method of Computation.*—The anteroposterior and the lateral roentgenographs are placed before illuminators and the usual observations regarding abnormalities, presentation of the fetus, type of pelvis, degree of engagement of fetal head, etc., noted. The circumference of the fetal skull as shown in the anteroposterior roentgenogram (Fig. 6) is measured by tracing the perimeter of the image as outlined.

The pointer on the pelvicephalometer is set at zero and the rotor traced around the periphery of the skull image in a counterclockwise

direction. The distance from the fetal skull to the table top in the anteroposterior direction is determined by measuring on the lateral roentgenograph (Fig. 6) the distance in centimeters from the center of the fetal head to the spine of the sacrum (K-M, Fig. 6), the

tients were examined by external measurements and compared with roentgenographic images of the pelvis. It was found that the thickness of the soft tissue was about equal to the increase in size of the bone image on the roentgenogram (usual magnification).

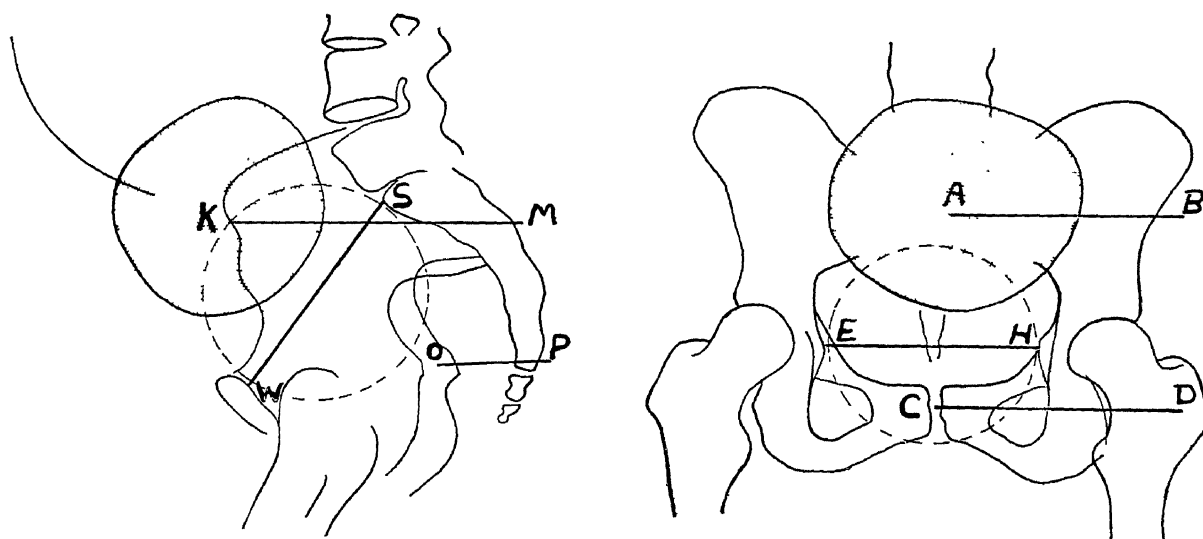


Fig. 6.—Anteroposterior and lateral roentgenograms of a near term pregnant woman with fetus in cephalic presentation left occipito-anterior position. Outline of roentgenographic anatomy used to illustrate method of computing *fetal cranium—smallest pelvic diameter ratio*. (Ball: Surg., Gynec. and Obst.)

line of measurement being the path of the central ray when the anteroposterior roentgenogram was exposed. The distance from the table top to the film (Fig. 7) then must be added to determine the total distance from the fetal head to the film.

The points *A-B*, *C-D*, *K-M*, and *O-P* in Fig. 6 are arbitrarily selected after many pa-

Therefore, the distances *A-B*, *C-D*, *K-M*, and *O-P*, in Fig. 6, were found to be accurate enough for clinical purposes to determine the distance of the object from the film when the table top to film distance was added to this measurement.

The two measurements of the perimeter of the fetal skull represent the circumferences of

a spheroid; from them the mean circumference must be determined to calculate the volume of a sphere. After this circumference has been determined, 2 cm. are added to allow for the soft tissues of the scalp, which allowance has been found to be the average scalp thickness. The volume of the fetal head then is read from the outer table on the calculator—*volume from circumference*.

Two pelvic diameters then are determined. The anteroposterior—true conjugate—is measured in the lateral roentgenogram, *W-S* in Fig. 6, by tracing the rotor of the pelvicalometer in a straight line from the antero-

coccyx or lower sacrum, *O-P* in Fig. 6. The linear magnification then is corrected by the use of the calculator.

The volume capacity of the pelvic diameter then is translated into a sphere of this diameter by reading the inner table on the calculator—*volume from diameter*. The broken circles in Fig. 6, graphically represent the midplane of this sphere.

The author has published several case history reports with x-ray films and measurements. Fig. 8 is an example of one of these.

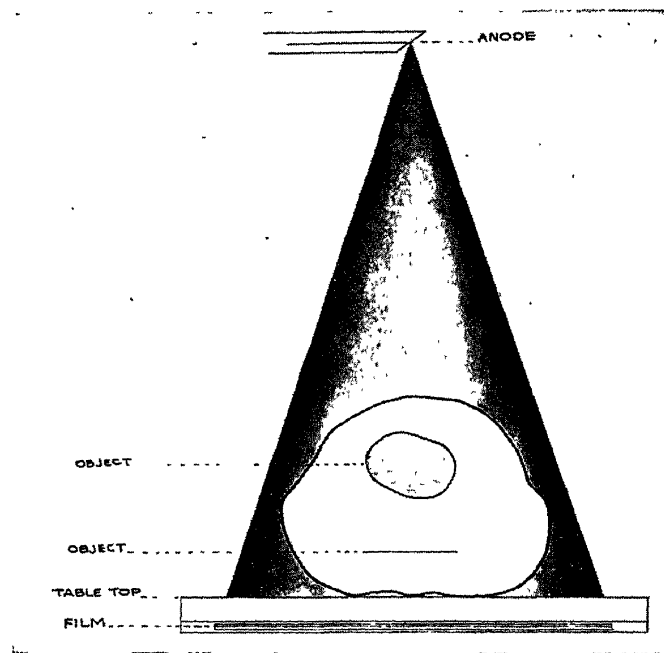


Fig. 7.—Drawing illustrating roentgenographic magnification. (Ball: Surg., Gynec. and Obst.)

superior border of the promontory of the sacrum to the posterior border of the symphysis pubis. The posterior border of the symphysis pubis is recognized by the posterior cortex of the pubis. The correction for the object film distance of this diameter is made by measuring on the anteroposterior roentgenogram the distance from the symphysis pubis to the plane of the midline of the greater trochanter, *C-D* in Fig. 6. The correction is made on the calculator and the pelvic diameter is read. The other pelvic diameter, measured in a similar manner is the biischial spine diameter, *E-H* in Fig. 6. The object film distance of this plane is determined from the lateral roentgenogram by measuring from the ischial spine to the posterior border of the

The author submits a graph (Fig. 9) from which the weight of a fetus *in utero* may be calculated from the measurement of the mean circumference of the fetal head. As there are rather large variations from the average, this calculated body weight is only fairly reliable in normal cases. It might have some value in predicting the chances of survival of premature infants.

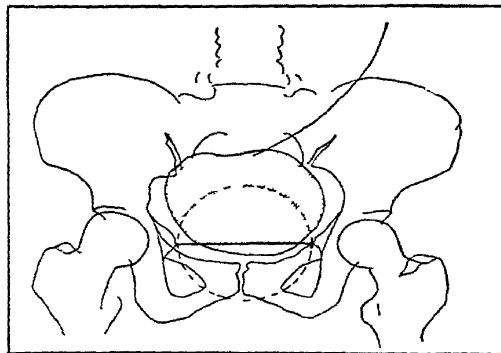
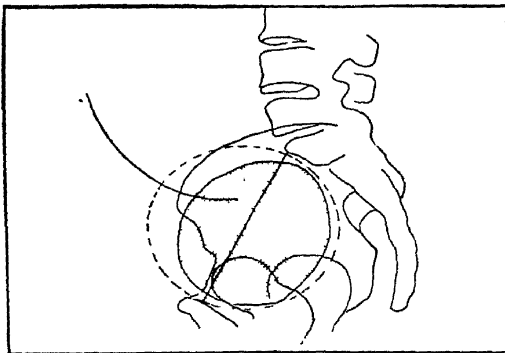
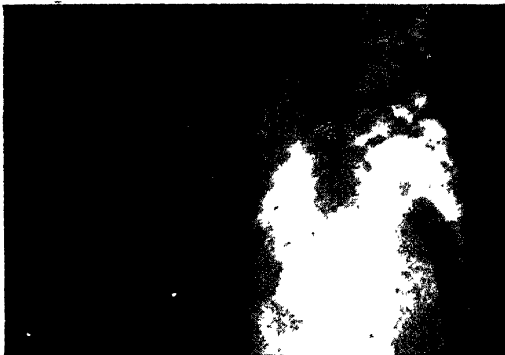
**Cholecystography.**—R. McWhirter (Brit. J. Surg. 23:155 (July) 1935) gives in detail the technic employed at the Mayo Clinic in cholecystography.



Oral administration seems to give as good results as intravenous administration, provided the technic is followed exactly. The dye must be given in sufficient quantity and in a readily absorb-

The author has analyzed 732 cases seen at the Mayo Clinic in 1932 in which the cholecystographic findings were checked at operation. Gall-bladders reported as "poorly functioning" and

|                                     |            |            |   |                 |        |  |
|-------------------------------------|------------|------------|---|-----------------|--------|--|
| Name                                | Chart No.  |            |   | X-Ray No. 31233 |        |  |
| Age 26                              | Race WHITE | Weight 160 | Height                                      | Gravida 2       | Para 1 |  |
| Last menstrual period MAR. 18, 1934 |            |            | Estimated date of confinement DEC. 24, 1934 |                 |        |  |



## ROENTGENOGRAPHIC EXAMINATION

| Date   | Presentation<br>Pos. | Type of Pelvis | Circumference of Cranial Skull |      |      | Pelvic Diameters |                 | Vol. Cap.<br>smallest<br>pel. dia. | Vol. of Head<br>Plus Scalp | Approx.<br>Weight |
|--------|----------------------|----------------|--------------------------------|------|------|------------------|-----------------|------------------------------------|----------------------------|-------------------|
|        |                      |                | A P.                           | Lat. | Mean | A P.             | Buscholz Spines |                                    |                            |                   |
| 1/2/35 | L.O.A.               | 1+             | 30.4                           | 31.8 | 31   | 11.5             | 10.6            | 610                                | 600                        | 7-10              |

## POSTPARTUM DATA: BIRTH

| Date   | Hours Labor |     |     | Type of Delivery | Amount of Head Molding | Circumferences |       |      | Volume | Sex | Weight |
|--------|-------------|-----|-----|------------------|------------------------|----------------|-------|------|--------|-----|--------|
|        | 1st         | 2nd | 3rd |                  |                        | S O B.         | O. P. | Mean |        |     |        |
| 1/2/35 | 3           | 30' | 10' | SPONT.           | NONE                   | 31             | 33    | 32   | 550    | F   | 7-1    |

Fig. 8—Illustrating case report of different positions of fetus. Shows accuracy and reliability of technic described. (Ball: Surg., Gynec. and Obst.)

able form. It must not be given alone on an empty stomach, but along with fruit juices, preferably grape juice. Fats must not be taken either before or at the time of ingestion of the dye.

"nonfunctioning" were thus described in terms of the pathology found at operation. Some of the cases proved that a cholecystogram might show apparently normal biliary function even when there

was extensive and serious disease of the liver. Also, a well filled gall-bladder and normal biliary function might be seen in cases of ulcer of the stomach and duodenum. On the other hand, delayed emptying of the gall-bladder did not necessarily indicate any diseased condition. Calcified gall-stones are a more definite indication for operation than gall-stones which are not calcified. The evidence showed that only 1 per cent.

with cystoscopic examination, observation of excretion of indigocarmine from the two ureters, and retrograde pyelography. Excretory urography fails to give adequate information in the following conditions:

1. When both kidneys are normal and excrete the dye so rapidly that shadows are not obtained.
2. When there are such extensive destructive changes in the renal paren-

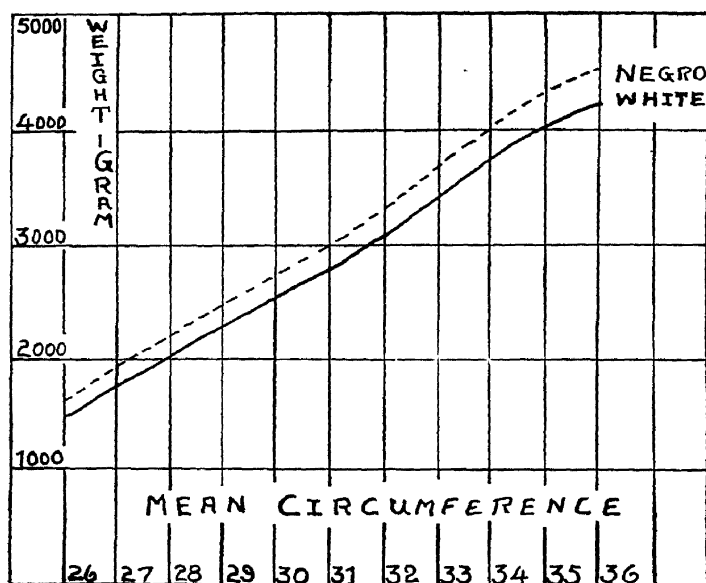


Fig. 9.—Graph showing average weight of newborn in relation to mean circumference in centimeters of fetal cranium. (Ball: Surg., Gynec. and Obst.)

of cases of gall-stones have carcinoma of the gall-bladder.

**Urography.**—In excretion urography, M. Swick states that the opaque substances which have been used successfully are *iopax*, *skioldan*, *neoskioldan*, and *hippuran*. Excretion urography has been of great help in establishing the diagnosis in many cases where retrograde pyelography has been contraindicated or difficult.

In discussing the necessity for both excretory and retrograde urography under certain conditions, D. N. Eisen-drath (Brit. J. Urol. 7:124 (June) 1935) cites cases to prove the necessity of supplementing excretory urography

chyma that there is no excretion of the dye.

3. When there is inhibition of renal function as the result of either acute blocking of the ureter or transitory paralysis of the nerves of secretion due to acute hyperemia.

As an example of the value of information obtained from as many methods as possible, the following case is reported: Excretory urography revealed *hydronephrosis* of the left kidney, but the relationship to the urinary tract of a shadow in the region of the kidney could not be determined by that method. A retrograde pyelogram showed that the cause of the hydronephrosis was a kink

in the ureter, and that the shadow was in the lowermost calyx of the kidney.

**Radiography of Soft Tissues.**—Refinements of technic must be employed in order to differentiate soft tissues. The first essential, according to J. R. Corty, is to use the lowest voltage which will give adequate penetration. Regions of the body as, for example, extremities, present 3 zones: (1) Skin, superficial fat and fascia, very small vessels; (2) muscle structures, large vessels, nerves, and periosteum; (3) solid bone.

Some of the uses of soft tissue roentgenography are in demonstrating the *vascular system, soft tissue tumors, muscle groups, calcification within muscles, ruptured muscles, soft tissue infections* (especially if presenting striking characteristics, as for example, *gas gangrene*), *bone-forming tissues* (*callus, inflammatory and malignant changes in periosteum*), *gall-bladder* (cholecystography), masses in the *abdomen, larynx* (foreign bodies, tumors, etc.)

**Diseases and Injuries of Skull.**—In reviewing the roentgenography of the skull, W. H. Coldwell pointed out that good x-ray films taken in standard positions may be of great help to the physician in the diagnosis of anencephaly, hydrocephalus, meningocele, microcephaly and oxycephaly. Similarly, good films may help in establishing the diagnosis in developmental as well as acquired bone conditions, such as *craniotabes, rickets, osteitis deformans, osteitis fibrosa cystica, Paget's disease, leontiasis ossium, multiple myelomatosis, periostitis, osteomyelitis, and syphilitic osteitis*. Fractures of the skull may appear in the radiograph as linear cracks, depressed portions of the bone, or detached areas of bone. Primary *neoplasms* in the cranial bones are uncommon, but *metastases* are much more frequent, especially from carcinoma of the breast and

thyroid. The outline of the *sella turcica* is examined in suspected *pituitary disease* and the position of the *pineal gland* may help in locating *cerebral tumors*. *Ventriculography* is an aid in the determination of *hydrocephalus* and certain kinds of *cerebral tumors*. *Lipiodol* may be injected into various *sinuses* to demonstrate the presence of *polypi* and other protruding masses. The commonest use of x-rays of the skull is in the examination of the *mastoids* and *sinuses*.

**Tumors of Bladder.**—Pfahler and Vastine advocate the employment of *pneumocystography* in addition to cystoscopic examination. Air is injected into the bladder previous to taking x-ray pictures. By this means tumors of the bladder may be demonstrated. An increase or reduction in size may be shown if the pneumocystography is done at intervals.

**Tumors of Kidney.**—Nichols states that *excretion urography* has thrown an additional responsibility upon the roentgenologist, who now, in order to pass his judgment upon urograms, must be a good clinician and understand the functional activity of the kidneys. The urograms must be interpreted in comparison with the normal in order to determine their degree of abnormality. Excretion urography is a valuable supplement to cystoscopy, catheterization of the ureters, and retrograde pyelography.

In *pneumopyelography* air is injected previous to roentgenography. The pelves and calices are thus rendered more translucent. *Calculi* or *tumors* may thus be made to stand out in relief.

In *pyeloscopy* preliminary *excretory pyelography* is done and then atropine is given in dosage large enough to relax the pelves of the kidneys so that they will distend as the urine accumulates in them. Another intravenous injection of dye is given and more roentgenograms are taken to ascertain if the distended

pelves can furnish more information than could be gained from the original urograms.

Tumors of the kidney are grouped as follows: *Hypernephroma*, *carcinoma* and *mixed tumors*. Nichols uses Ewing's classification of tumors of the renal pelvis: (1) *papilloma*, (2) *papillary epithelioma*, (3) *alveolar carcinoma*, (4) *squamous cell carcinoma*.

Various lesions outside the kidney may press upon it and interfere with its function or may simply crowd it out of its normal position.

**X-RAY SICKNESS.**—Three types of x-ray sickness are recognized by G. W. Holmes and G. T. Hunter: (a) toxic sickness, (b) psychic sickness, (c) true x-ray sickness. *Toxic sickness* may be due to failure of the liver to detoxify the split proteins resulting from irradiation. The *prevention* of this type of sickness consists in the **avoidance of large amounts of irradiation at any one time**. Its *treatment* consists in the stimulation of **elimination, increase in fluid intake, rest**, and in some cases, intravenous injection of **glucose solution**.

*Psychic sickness* does not vary in direct ratio to the dosage of irradiation and is most common in high-strung nervous individuals.

*True x-ray sickness* is treated on the assumption that temporary disturbance of the liver function is the underlying cause. A **high carbohydrate diet** with **adequate fluid intake** is prescribed. Candy and fruit juices sweetened with extra amounts of lactose may be given between meals. If patients are unable to take enough food by mouth, **glucose** may be given intravenously, 1500 c.c. of a 5 per cent. solution twice a day.

**X-RAY INJURIES TO SKIN.**—Radiologists, in general, believe that there is no such thing as idiosyncrasy to x-rays, but normal healthy skin in different individuals may vary 10 to 15

per cent., according to G. S. Zugsmith. Injured skin is more sensitive than normal skin and the same may be true of the skin in individuals with syphilis, Bright's disease and other toxic conditions. Certain chemicals on the skin increase its sensitivity, among which may be mentioned iodine, scarlet R, mercury, pyrogallic acid, cantharides, resorcin, betanaphthol, tar, iodoform, sulphur and salicylic acid. Areas of increased heat and moisture, such as the axilla, groin, perineum, and fatty folds of the obese, are more sensitive than dry areas. The most susceptible type of individual is the one with fair and ruddy complexion, red hair and a thin skin.

There are 3 degrees of x-ray cutaneous injury.

In the *treatment of x-ray dermatitis* some radiologists use **actinic or ultra-violet light**, but others believe this may do more harm than good. **Mild lotions and ointments** are recommended but caustic irritants and harsh antiseptics should be avoided.

In more severe cases, which have not healed in 3 months, **amputation** may be indicated or **excision of the injured skin** with subsequent **skin grafting**.

**RADIUM AND X-RAYS.—TECHNIC.**—*X-ray Therapy by Chaoul Method.*—In discussing this form of x-ray therapy, E. P. Pendergrass (Am. J. Roentgenol. 35:101 (Jan.) 1936) states that the Chaoul method is justified by the need of using x-rays instead of radium where the latter is unobtainable because of its first cost. Comparatively low voltage (50 to 60 K. V.), short distance (3 to 5 cm. target skin distance), shock-proof apparatus and special design of tube are essential features. Metal applicators are placed over the anode end of the tube and may be brought into direct contact with the skin so that the target-skin distance is only 3 to 5 cm. Special

applicators are supplied for insertion into body cavities.

The source of high tension employed is a simple constant potential generator (Siemens "monopan"), using a Greinacher circuit and having a maximum output of 60 K.V. and 4 ma. The tube has been described by Ernst, Frik and Ott. It is so designed as to have the source of radiation at one end of an

Chaoul now gives a daily dosage of 400 r per field and may treat several fields the same day. This may be repeated every day until each field has received 5000 to 6000 r. In some cases the total dosage may be as much as 20,000 r per field spread over 15 days. Small fields of 10 to 20 sq. cm. are used. The higher dosages may cause sloughing of the skin, but healing follows rapidly with epitheli-

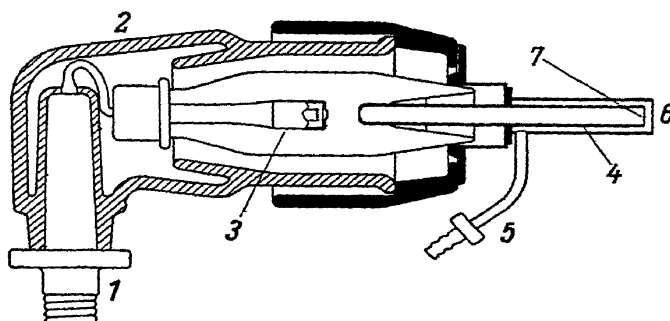


Fig. 10.—1. High tension current. 2. Porcelain shield to tube. 3. Cathode. 4. Anode. 5. Water cooling lead. 6. Aperture for rays. 7. Focal spot. (Ernst, Frik and Ott: *Strahlentherapie*; Pendergrass: *Am. J. Roentgenol.*)

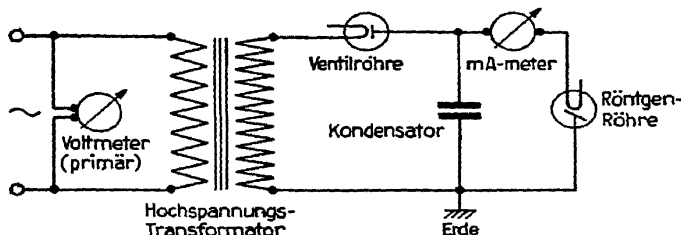


Fig. 11.—Drawing of Greinacher circuit. (Ernst, Frik and Ott. *Strahlentherapie*; Pendergrass: *Am. J. Roentgenol.*)

earthed metal tube, the rays emerging through the target of gold-plated nickel and the water cooling jacket. These factors constitute the filter usually employed and, according to Morison, Hugo and Mayneord, is equivalent to approximately 0.2 mm. nickel. The mean wave length is roughly 0.32 Å.

The output with the factors above is about 110 r/min. measured in air. If the usual back scattering is included, the dosage rate is about 130 r/min. This dosage rate is approximately 25 times as great as that delivered by a 1 gram radium "bomb" at the same skin distance.

zation from the periphery. Occasionally an intense purple erythema appears before treatment is completed, which should be a warning to discontinue treatment. In cases where the cancerous tissue has not entirely disappeared after one course of treatment, a second course may be begun after an interval of 3 or 4 weeks.

According to Chaoul, this method of low voltage irradiation should not be given over skin areas which have previously received radium treatments or x-rays at the conventional higher voltages, because of the danger of delayed

radiation effects. Other radiologists believe that it is safe to use Chaoul's method if several months have elapsed since the other treatment was finished. Chaoul uses the low voltage x-rays for superficial lesions, but for deeply situated cancers he favors 180 K.V., target-skin distance 10 cm., filter 0.5 mm. cu., field 28 sq. cm., dosage 150 to 200 r daily, usual total dose 3000 r and never exceeding 5000 r.

Chaoul states that deep seated lesions present an opportunity for coöperation between the surgeon and the radiologist. A good example is a patient with *rectal carcinoma* in whom the surgeon may do a preliminary *colostomy* and then resect the *coccyx* and lower portion of the *sacrum*, thus exposing the cancer. The wound is packed and kept open so that the cancer is accessible for contact x-ray treatment. Chaoul believes that this coöperative way of treating patients will progress and that special x-ray tubes will be designed to treat various regions which may be exposed by surgical methods.

**Telecurie Therapy.**—The treatment of *malignant tumors* by *gamma* rays from radium at a distance of 5 to 10 cm. from the skin is called telecurie therapy. This method requires large amounts (1 to 5 grams) of radium, the treatments lasting many minutes or several hours. The advantage of telecurie therapy, according to Schreiner, Reinhard and Wehr, is due to the fact that in treating malignant disease in deep tissues, the skin is not affected as much with the radium at a distance as when it is in close contact. The law of physics applying in this case states that the greater the radium skin distance (R. S. D.), the greater the percentage of depth dose. The depth dose decreases when the radium is moved farther away from the skin, but not as much as the skin dose decreases at the same time. An

apparatus has been devised in which 3 radium cannon are used simultaneously so as to treat deep seated malignant growths by converging 3 beams of gamma rays upon the tumor. The skin effect is reduced by this means, as the gamma rays traverse 3 separate skin portals. This apparatus is proving especially useful in treating *malignant growths* in the *rectum*, *bladder* and other relatively inaccessible locations.

**THERAPEUTIC USES.—Malignant Growths.**—Levitt considers that not all cases of malignant disease should be given x-ray treatment and the radiologist must try to distinguish between cases that may be benefited and those in which the x-rays will prove of no value. Malignant growths differ widely in their *radiosensitivity*, which is the relative ease with which their cells can be killed in comparison with cells of normal tissue. A malignant growth which is radiosensitive has a considerable margin of safety between the dose required to kill its cells and that required to kill the normal cells in surrounding tissue. If a malignant growth is not radiosensitive, a dose of radiation great enough to kill its cells would also kill the cells of normal tissue adjacent to it. It can readily be appreciated that very accurate dosage of radiation has to be applied in treating malignant tissues which are only moderately radiosensitive.

Another factor which influences the radiologist in his decision regarding the treatment of a malignant growth is its *distribution*. This may be considered under 4 headings:

- (a) Primary growth only discoverable.
- (b) Primary growth, with metastases in regional lymphatic gland.
- (c) Primary growth, with or without regional metastases, but with an apparently isolated distant secondary deposit.
- (d) Cases in which the disease has become generalized.

**PRINCIPLES GOVERNING RADIATION THERAPY OF CANCER.**—In a discussion of the treatment of cancer by irradiation, G. T. Pack (Am. J. Roentgenol. 36:233 (Aug.) 1936) states that surgery, the actual cautery, and chemical cauterizing agents all have their place in removing or destroying cancerous tissues. Radiation therapy, by x-rays and gamma rays from radium, has definite advantages over these other methods in cases of cancer, in which the cancer cells are more easily killed than are the cells of the normal surrounding tissue. Radiosensitivity seems to have some relationship to the origin of the cells making up the cancer. Tumors developing from primitive blood-forming tissues are likely to be radiosensitive, as for example, lymphosarcoma, myeloma, endothelioma and angioma. Tumors developing from neural crest cells are likely to be radioresistant, as for example, glioma, neurosarcoma, melanoma and mixed tumor of the parotid.

**Methods of Radiation Therapy.**—Irradiation therapy may be applied by 2 methods: (1) From an external source, and (2) from a source applied directly into the tumor or surrounding it. External radiation may be given by x-rays with low voltage for superficial lesions and with high voltage or supervoltage for deeply seated lesions. Radium may be used instead of x-rays for the treatment of superficial lesions by means of small plaques, trays or moulages. Radium may be used for deeply seated lesions (teleradium therapy) by means of large quantities of radium in bombs or packs several centimeters away from the lesions under treatment.

**Intracavitary Irradiation.**—Radium element in tubes, covered with sufficient platinum, gold, brass or aluminum for filtration, may be placed within body cavities for contact treatment of cancers

of nares, orbits, antra, larynx, esophagus, uterus or vagina.

**Interstitial Irradiation.**—Radium needles and radon seeds may be driven directly into or placed in groups surrounding cancers in soft tissues. This method of treating accessible tumors is usually supplementary to external irradiation.

**Units of Dosage.**—Pack has summed up the dosage used in irradiation therapy concisely in the following words: "It is best to administer to all the neoplastic territory the maximal quantity of radiant energy compatible with the maintenance of tissue integrity. To speak intelligently of these quantities it is best to have some common physical and biological measures of the dosage. Thus in the case of radium, the quantity of gamma rays at the source is known as the dose of emission. One knows with precision the dose of emission because this is invariable. The dose emitted is expressed by two different notations. The one has for its basis the intensity of the gamma rays and the duration of their application; the intensity is proportional to the quantity of radium present; the dose is obtained by the product of the quantity and the time, which is expressed as milligram-hours of radium or as millicurie hours of radon (gram-hours or curie-hours in the case of large radium bombs or packs). The other notation, which is utilized throughout France, makes the dose proportional to the quantity of radium emanation destroyed (disintegrated) during the course of its application. This is expressed in terms of 'millicuries-destroyed or of microcuries-destroyed,' the latter term connoting only one-thousandth of the former. The physical efficiency of 1 millicurie of radon throughout its life is equivalent to 133 millicurie-hours. Therefore 1 millicurie-destroyed is equivalent

to 133 millicurie-hours or 133 milligram hours.

"The dose of gamma or roentgen rays at the surface or the point of entrance into the body is the superficial dose, while the dose to the tumor by unit volume of the tissues treated is the 'tissue or tumor dose.' The unit of x-ray dosage called the 'roentgen' or r (designated always by small r) has been standardized and internationally accepted. The roentgen has been defined *as that quantity of roentgen radiation which, when the wall effect of the ionization chamber is avoided and the secondary electrons are fully utilized, produces in one cubic centimeter of atmospheric air at 0° C. and 76 cm. mercury pressure such a degree of conductivity by ionization that one electrostatic unit of charge is measured at saturation current.*

"In the measurement of roentgen rays and gamma rays by biological means, the most common unit is the establishment of an erythema dose under certain conditions. Quimby of the Physics Department of the Memorial Hospital has defined and employed the term, 'threshold erythema,' which is that dose of radiation that will cause a perceptible change in the skin of 80 per cent. of the subjects and no discernible discoloration in 20 per cent. in 2 to 4 weeks after the exposure to the rays. Quimby has found that the threshold erythema with 200 Kv., 100 sq. cm. field, 50 cm. target-skin distance, and filter of 0.5 mm. copper and 2.5 mm. aluminum is 500 to 525 roentgens. The therapeutic erythema, on the other hand, varies with different radiologists from 600 to 1000 roentgens."

*Tissue Dose.*—Cancericidal Dose.—At the Memorial Hospital the "threshold erythema" is used as the unit of tissue dosage. As mentioned above, this can be determined for each x-ray tube and

each radium applicator by direct experiment. At various depths below the surface of the tissue being irradiated, the depth doses can be calculated as being various percentages of the dosage of the radiation falling on the surface. The method of determining these percentages is by making measurements with a small ionization chamber placed first on the surface of a vessel of water and then placed successively at various depths below the surface of the water. Such water phantom measurements agree fairly well with measurements obtained by placing the ionization chamber similar distances beneath the surface in various cavities in the human body. The data obtained by these water phantom measurements are plotted as "isodose curves." These isodose curves are used for rapid calculation of the depth dosage given to a tumor when irradiated by cross firing through several portals.

In the case of interstitial irradiation, the measurement by direct experiment is more complicated, especially as the irradiation is applied from numerous sources simultaneously. At Memorial Hospital, this has been worked out in a practical manner by Martin and Quimby. They have demonstrated that *in any sphere, it makes little difference in the dosage at the periphery whether the source of radiation be concentrated at the center or be distributed uniformly within the inner half of the sphere.* They have prepared tables for spheres of various sizes, giving threshold erythema dosages at the periphery when various quantities of radon are placed near the center or at least within the inner half of the spheres. The cancericidal doses for many different kinds of tumors have been determined by actual clinical observation and can be stated in terms of threshold erythema dose (T.E.D.). For example, intraoral squamous cell carcinoma requires 6 to 8 T.E.D., while transitional cell carcinoma



requires 2 to 4 T. E.D. for sterilization. By calculating external irradiation and interstitial irradiation in terms of the same unit, it is convenient then to determine combined external and interstitial irradiation by adding the number of units applied in the two methods.

*Prescription for X-ray Therapy.*—For the safety of the patient x-ray dosage must be prescribed in an accurate way and a detailed record should be kept of the treatment given. The quantitative factor should be expressed in r units and the qualitative factor in Angstrom units or by stating the half-value layer in millimeters of copper, aluminum, or other metallic filters. In addition to these two factors the kilovoltage, filtration, target-skin distance, and time of application in minutes should be specified. The tumor depth below the surface should usually be indicated. The size and number of the portals through which treatments are given is also important, as is also the factor of number of treatments, and the intervals between treatments, for a single massive dose has an effect quite different from that of the same total dosage fractionated over several weeks or months.

*Kilovoltage (Potential).*—As the kilovoltage or potential applied to the x-ray tube is increased, the average wave length of the rays emitted becomes shorter and shorter. Short waves penetrate tissues more readily than longer waves. This important factor is utilized in therapy of tumors deep below the surface by applying high voltages of 200 K.V. For therapy of superficial skin diseases lower voltages are used. All x-ray tubes give off rays varying considerably in wave length. When the effect of short waves on deep tumors is desired, filters of copper, aluminum or other metals are employed, to absorb the long waves which would have an un-

desirable effect on the skin and superficial tissues.

*Comparison of Teleradium Therapy with Supervoltage X-ray Therapy.*—It has been estimated that supervoltages of over 1500 K.V. would produce x-rays having wave lengths comparable to the gamma rays of radium. Already there are several 1000 K.V. (million volt) machines in use in the United States. The x-rays produced by these machines have biological effects differing little, if any, from the effects which follow teleradium therapy with packs, containing 4 grams of radium. The x-rays have far greater intensity and so can be used to treat more patients in a given time. This greater intensity may not be desirable however, for therapy spread out over a longer period seems to have advantages.

*Effective Wave Length of Radiation.*—The wave length of x-rays depends upon 2 factors, (1) the energy with which the electrons fly across the x-ray tube and bombard the target, and (2) the atomic weight of the material of which the target is composed. The energy with which the electrons fly across the tube increases with the voltage applied to the terminals of the tube. The wave length of the x-rays becomes shorter as the voltage is increased. The higher the atomic weight of the target material, the shorter the wave length of the x-rays emitted. Tungsten, of which most targets are made, has a very high atomic weight and emits characteristic rays of very short wave length. When x-rays emitted by the tungsten target enter the human body, they encounter secondary targets of much lower atomic weight, such as sodium, potassium and calcium. The secondary rays given off from these targets have much longer wave lengths and feeble penetration than the original rays. It is apparent that the way to get

deep penetration, to deliver greater depth dosages, is to raise the voltage applied to the x-ray tube. To put this into figures, Pack gives the following: "Failla has found that the relative depth doses at 10 cm. depth obtained under comparable conditions with 200 K.V. x-rays, 700 K.V. x-rays and gamma rays, are respectively 29.0, 41.2 and 56.7 per cent. Accordingly, from this point of view, 700 K.V. x-rays are considerably better than 200 K.V. x-rays, but not as good as gamma rays. This advantage is not realized in clinical practice because it is not practical to apply radium at the focal distances used in x-ray therapy."

*Ionization in Tissues.*—The destruction of living cells by radiation is due to the release of electrons from the atoms, of which the cells are composed, when these atoms are bombarded by gamma rays or x-rays. Finally, the atoms, minus one or more electrons, combine with other electrons. In some cases the recombination is harmless to the cell, but in other cases the recombination is a form of chemical change which brings about the death of the cell.

*Current Milliampereage.*—The kilovoltage applied to the terminals of the x-ray tube determines the speed with which the electrons fly across the tube and strike the anode and determines the wave length of the x-rays emitted. In a similar manner the milliampereage is an indicator of the number of electrons flying across the tube. The more electrons flying across the tube, the more x-rays are emitted from the anode in a given length of time. Pack states this concisely in the following words: "The usual roentgen tubes carry from 4 to 30 milliamperes. Thus a tube running at 4 milliamperes for 25 minutes would deliver 100 milliampere-minutes and a tube running at 25 milliamperes for 4 minutes would also deliver 100 milliampere-minutes or its equivalent in

roentgens, other conditions remaining the same."

*Filter.*—As previously mentioned, high velocity x-rays, which have short wave lengths, penetrate more deeply into body tissues before their energy is expended than do x-rays of lower initial velocity and correspondingly longer wave lengths. Conversely, low velocity x-rays, which have long wave lengths, expend their energy on the skin or superficial tissues and do not penetrate to the deep tissues. When tumors far beneath the surface are to be treated, it is necessary to interpose filters of copper, aluminum or other metals to absorb the rays of long wave length and thus protect the skin and superficial tissues. The waves of short wave length pass through copper and other metals if the filter is comparatively thin. The number of millimeters of copper or other metal which will cut down the intensity of an x-ray beam to one-half of its initial intensity is called the "half-value layer." It is an indicator of the quality or wave length of the beam. Another way of expressing the effective wave length of the beam is to give the measurement in Angstrom units. The author gives the following data to illustrate:

"Failla and Quimby have found that the effective wave length employed in the usual deep roentgen therapy at the Memorial Hospital is about 0.16 Å. This treatment is given with 200,000 volts (peak) filtered by 0.5 mm. Cu. and 1 mm. Al. With intermediate voltage of 140 K.V. the filter may vary from nothing up to 6 mm. of aluminum; with a filter of 4 mm. Al. the effective wave length is about 0.25 Å.

"In the case of radium, the filters employed, usually brass, lead, silver, gold or platinum, are usually expressed in the equivalents of certain thicknesses or its equivalent (occasionally 0.5 mm. of platinum. One millimeter of platinum

platinum) is the customary filter for surface application of radium or tele-radium therapy. Intracavitary radium treatments are given with filters of 0.5 to 1 mm. of platinum, while interstitial irradiation requires considerably less filtration. Gold radon seeds have a wall thickness of 0.3 mm. gold and most platinum needles for interstitial use are designed with a wall thickness equivalent to 0.5 mm."

*Size of Irradiation Field.*—When x-rays and gamma rays strike the human body, their energy is absorbed by the atoms of which the tissues are composed and rays of longer wave length are given off in various directions. These oblique rays, in turn, strike other atoms and are given off again in various directions and at still longer wave lengths. After these secondary rays have struck many atoms successively, the rays have been scattered in all directions and many of them are even going in the opposite direction from that of the initial rays. In this manner the skin and superficial tissues are bombarded in all directions by the initial rays plus the scattered secondary rays. It is quite easy to picture this mentally and to comprehend that the larger the areas treated by irradiation, the more the scattered rays from portions of the initial beam will overlap the scattered rays from other portions of the beam. The scattered rays may amount to as much as 40 per cent. of the total irradiation in the skin and superficial tissues. At a depth of 10 cm. the scattered irradiation may amount to 80 per cent. if the area treated is large. This is a very important fact to be considered in planning deep therapy. Large concentration of irradiation in deep tumor tissues may be obtained and at the same time skin dosage kept within the limits of toleration, by using small portals and directing

the beam accurately at the tumor from several different directions.

*Target-Skin or Radium-Skin Distance.*

—Pack has presented this distance factor so concisely that it is quoted: "The inverse square law of radiation states that the intensity of a beam of roentgen rays or gamma rays varies inversely proportional to the square of the focal-skin distance from a point source. Thus the radiation intensity from a high voltage roentgen tube at 50 cm. distance is almost twice that delivered at 70 cm. focal-skin distance. Or a radium applicator placed at 2 cm. radium skin distance conceivably would deliver 4 times the superficial dose as the same applicator applied for the same time at twice the distance, or 4 cm. (This is not exactly true since the radium applicator is not a point source.) This fact may be expressed also in the following manner. Since the dose is dependent on the product of the intensity times the duration of exposure, the radium treatment at 4 cm. distance would require 4 times as many minutes or hours as at 2 cm. radium-skin distance. The question naturally arises, why not decrease the focal-skin distance as much as possible to save time and expense? In the case of very superficial noninfiltrating skin cancers this plan is feasible, but for the more deeply situated cancers the depth or tissue dose is increased (in comparison to the dose delivered to the superjacent skin and tissues) with the greater skin-target distance. Theoretically the distance might be increased sufficiently so that the relative dose on the skin at the portal of entry of the rays would be almost the same as at the location of the tumor within the body."

*Heublein Method of Continuous Irradiation.*—The theoretical increase of target-skin distance to such great distance that the tumor dose and skin dose

will be almost the same has been put to experimental trial by Heublein and Craver at the Memorial Hospital. The x-ray tube was placed 24 feet away from patients lying in bed. The tube was operated at 185 K.V. and 3 ma. The time required to deliver 225 r at 24 feet was 250 hours or 12.5 days at 20 hours a day. The clinical skin erythema dose of 750 r (measured in air) was the unit of dosage employed. One hundred and thirty-four cases were treated in two years. These were mostly generalized and radiosensitive tumor processes, such as the *leukemias*, *lymphosarcoma*, *Hodgkin's disease* and *multiple myeloma*. The results in the treatment of chronic lymphatic leukemias and pseudoleukemia seemed superior to any obtained previously by local irradiation. The treatments were given cautiously at first and dosages were eventually increased to 375 r to 450 r. There were no complications resulting from the irradiation, except the occasional development of leukopenia, anemia and thrombocytopenia in some cases. This is considered to be one of the most important achievements in radiation therapy in the last decade. Its principles of low intensity, great distance, continuous irradiation and long duration of treatment may be found of value in the therapy of many cancers which have been refractory to other methods.

*Time-Intensity Factor.* — Satisfactory irradiation treatment in the cure of any cancerous condition involves the adjustment of dosage so that the cancer cells will be destroyed and the normal tissue cells will be allowed to live. It might involve the prevention of reproduction of the cancer cells and allow reproduction of the normal cells. In the latter case, the cancer cells would simply die of old age, leaving the succeeding generations of normal cells in undisturbed occupancy. The dosage which

can be used in therapy is limited by the amount of radiation which the normal cells can receive and still continue to reproduce. Regaud, Coutard and Lacassagne performed some very important experiments which allowed them to draw conclusions regarding the method of irradiation which would kill cancer cells and allow the survival of normal tissue cells. Their test materials were rabbits, in which various dosages of x-rays were administered to the testicles and anorectal skin and mucosa. The rapidly developing spermatogonia resembled in many ways the rapidly developing cancer cells. The skin and mucous membrane were representative of normal tissue cells. It was found that the spermatogonia could not be killed by a single massive dose of x-rays without at the same time causing serious damage to the skin and mucous membrane. When the x-ray treatment was given in several fractional doses with a considerable interval of time between the doses, there was a great difference in effect; the spermatogonia were affected even more than by the single dose, while the skin and mucous membrane were affected less than by a single large dose. Pack states this in the following manner:

"Regaud's explanation of the superiority of continuous or fractionated irradiation over short intensive treatments is founded on the existence of alternating periods of radiosensitivity and of radioresistance in the life of the spermatogonia (in the experiments) and the cancer cells (in clinical practice). Spermatogenesis in a mammal such as the rabbit is a continuous phenomenon if the testicle is considered as a whole. But if one considers only a certain cell or line of cells on a seminiferous tubule, the function of reproduction by cell division is seen to be discontinuous and cyclic and the spermatogonia-like cancer

cells pass through alternating phases of multiplication (brief phase) and of rest (long phases). In one line of cells, either spermatogonia or cancer cells, the phase of multiplication corresponds to accentuation of radiosensitivity (law of Bergonié and Tribondeau), whereas the phase of rest corresponds to the diminution in radiosensitivity. A short treatment therefore might destroy only those spermatogonia or cancer cells which are dividing at that time; it spares the others. It is only natural that prolonged and continuous irradiation (in the case of radium) or well fractionated irradiation with proper spacing of the fractions into a fairly long time (in the case of roentgen rays) is more efficient than brief intensive irradiation, because in the first case the germinal or cancer cells are killed one after the other as the cycle progresses and these cells enter for the moment the phase of maximal radiosensitivity. These principles are now so generally recognized that the prolonged irradiation of low intensity or fractionated cumulative treatments have found almost universal favor with roentgenologists and radium therapists. These treatments depend usually on the administration of sub-erythema doses repeated every 24 or 48 hours until a total dose of 6 to 8 threshold erythema units may be delivered to one skin portal with perfect safety. To illustrate the application of this principle, let us consider the treatment of a hypopharyngeal carcinoma by high voltage roentgen rays only. Two lateral portals are used to crossfire the beams of radiation. With a single massive dose, only 850 r can be given to each side of the neck without seriously damaging the skin. By the fractionated method 300 r may be given daily, alternating on each side of the neck, until a total of 3000 to 4000 r are delivered through each portal. Such a

course of treatment requires 3 weeks to consummate the dose required to sterilize the carcinoma."

*Summary of Methods of Treatment.*—There are only 4 methods of treatment commonly employed.

1. The massive dose technic.
2. Saturation dose.
3. Fractionated dose.
4. Continuous irradiation.

The single *massive dose* was formerly used and was intended to destroy all the cancer cells at once. If, however, a few cancer cells survived, the cancer might grow again. If the dosage was just below the tolerance of normal tissue cells, the skin and superficial tissues would survive. A massive dose treatment could not be repeated for several weeks.

Kingery introduced the *saturation dose* method in the treatment of skin diseases by low voltage x-rays without any filter. He gave an initial erythema dose and then maintained the biological effect by adding smaller doses at proper intervals. He added 50 per cent. of an erythema dose after 3½ days to make up for the recuperation of the tissues from the initial dosage. Pfahler was the first radiologist to use this method in the treatment of cancer by properly filtered high voltage x-rays.

In the *fractionated dose* method, daily treatments are given with doses below an erythema dose. A cumulative effect is obtained. The cancer cells do not recuperate as quickly as normal cells from irradiation and so a cancericidal cumulative dose is reached before a cumulative dose lethal to normal tissue cells is reached. Also, as mentioned previously, the irradiation given in repeated dosage is more likely to destroy the rapidly multiplying cancer cells during their periods of cell division.

The *continuous method* of irradiation, as used by Heublein and Craver with

their teleroentgen equipment, is a further development of the method of fractionated small dosages. Treatment is given for 20 hours a day for several weeks with x-ray tubes 24 feet away from the patients.

**CANCER OF BREAST.**—The therapy of cancer of the breast has recently been reported in statistics from several well known hospitals. *Combined operation and irradiation* is the method of treatment advocated by the majority of radiologists and postulates thorough **radical mastectomy** followed by **irradiation** adequate to destroy all cancer cells in the bed of the tumor and surrounding tissues. Many radiologists confine their postoperative irradiation to the field of operation and axillary and supraclavicular regions. Other radiologists give prophylactic irradiation to the lungs, mediastinum and vertebral column. A. Gunsett follows **radical mastectomy** by surface mould **radium** to the axilla, radium needle implantation in the internal mammary lymph drainage region, and **x-rays** by a protracted divided dosage technic to the tumor bed, supraclavicular fossa, thorax and spinal column.

Different technic must be used in treating a primary carcinoma of the breast, a recurrence, or advanced metastatic disease, according to Pfahler and Vastine. The technic must be varied according to the stage, extent and type of the disease. In advanced cases, repeated examinations must be made of the chest, the mediastinum and the bones for metastasis. When any suspicious areas are found, they must be carefully irradiated. The sooner recurrences and metastases are discovered, the more hope there is of combating them. It is recommended that every patient with carcinoma of the breast be under observation for many years and be carefully examined at stated intervals.

*Preoperative Irradiation.*—A series of 81 cases of operable cancer of the breast is reported by F. E. Adair and F. W. Stewart (Ann. Surg. 102: 254 (Aug.) 1935) in which operation was delayed for several months in order to give irradiation previous to surgery. The 4 Gm. **radium pack** was used in 39 cases and high voltage (200 K.V.) **x-rays** in 42 cases. Breast and axilla were irradiated through 5 portals with the radium pack. Three to 4 months after this treatment, **radical amputation** of the breast was done and the tissues were carefully examined. In 11 (28 per cent.) of the 39 cases no trace of cancer tissue could be found. In 46 per cent. there were profound changes produced by the radium in the breast tumors. In cases with axillary node involvement, the radium had produced profound changes in the nodes in only 19.5 per cent. Because this indicated inadequate treatment, a new method was devised. A long forceps was introduced behind the pectoralis muscles and brought out near the sternoclavicular joint. The forceps was used to draw in a catheter containing 6 tubes of radon in tandem. By this means 3 to 7 skin erythema doses, 3 mm. from the radon, were delivered. It is yet too early to draw conclusions regarding this interstitial treatment.

In the 42 cases treated by the high voltage x-rays, complete microscopic disappearance of the tumor occurred in 7 (16.5 per cent.) of the cases. The dosage consisted of 1200 to 1800 r to each of 6 portals.

The authors conclude that preoperative irradiation will definitely increase the incidence of 5-year cures and should be employed in all cases of cancer of the breast in pregnant women, in cases with extensive axillary involvement, and the cases of young women.

**CANCER OF KIDNEY.**—In discussing the immediate effect of preoperative radiation in cortical tumors of the kidney, G. C. Prather and H. F. Friedman (New England J. Med. 215:655 (Oct. 8) 1936) state that patients with renal cortex tumors have an average life of 2 to 3½ years. Early diagnosis is unusual and about 5 per cent. of cases are too far advanced when first recognized to warrant surgical treatment. From 12 to 26 per cent. of cases when explored are found to be inoperable. The mortality rate following nephrectomy is from 15 to 30 per cent. in some hospitals. These figures will vary widely depending upon whether the surgeons are cautious or daring. The size of the tumor is one factor which makes surgery difficult.

In regard to the use of **x-ray** treatments **preoperatively** to reduce the tumors in size, to make them more easily removed by the surgeon, Prather and Friedman make the following statement:

"It has, therefore, been of the greatest interest to hear of the encouraging reports of Waters, Bothe and Wharton in the use of the Coutard type of preoperative irradiation to reduce the size of these tumors. Their clinical and histologic studies show that many tumors of the renal cortex will diminish in size in a spectacular manner. This has held true apparently in tumors composed of embryonal, poorly differentiated cells which lack a tough membrane. Bothe reports reduction in size of 40 to 50 per cent. in two mixed tumors of the kidney which he irradiated.

"The series of 15 cases reported by Waters, Lewis and Frontz has shown 93 per cent. radiosensitivity. Wharton reports 2 Grawitz hypernephromas and 2 Wilms' embryomas which decreased in size almost miraculously. To this group I can add 1 Wilms' tumor and 2 hypernephromas which were definitely reduced

in size by preoperative irradiation. A fourth case, carcinoma simplex of the adrenal, did not appear to be influenced. In the small number of cases reported to date, therefore, we have reason to be pleased with this method of temporarily reducing the size of cortical tumors of the kidney."

The authors point out that because tumors have been reduced in size, it does not necessarily signify that they have been cured. Bothe reported 3 cases, in children, in which tumors decreased in size, following irradiation treatment, to such an extent that the parents hoped that cures had resulted and would not permit surgery. Two of the three children were dead within a year. The *technic* of x-ray therapy used by Prather and Friedman (*Ibid.*) in the case of the Wilms' tumor was: 200 K. V. pulsating, 4 ma., 0.75 mm. Cu., and 1 mm. Al., 50 cm., wave length (effective) 0.16 Å units, 10.5 r per minute, 2 portals 150 sq. cm. each, 4000 r total dose, 200 r daily for 20 days alternating front and back. This dose was repeated to the kidney bed following operation. The patient was in poor condition and the dosage was about the minimum which would be effective in reducing a Wilms' tumor. In patients in better condition, larger doses are recommended.

In the treatment of a *hypernephroma*, the authors give the following details:

"Case 3 presented a huge mass in the right side of the abdomen and the typical roentgen findings of a cortical tumor. The lethal dose for a hypernephroma, in so far as we are aware, has never been determined. We have given as high as 9000 r directly into the mass through 3 fields of 180 sq. cm., anterior, posterior and lateral. This has produced a destruction of the germinal layer of the skin with denudation of the dermis. In the microscopic examination of this tumor one was able to distinguish

live tumor cells. There was considerable fibrosis and a great deal of necrosis. No intestinal symptoms were noted in any of our cases. The blood remained unchanged and the skin returned to its normal texture in two weeks. Two weeks following the irradiation, the tumor had decreased to half its size to be followed by an increase for a period of 10 days. We wish to call particular attention to this phenomenon which apparently is due to edema caused by the irradiation. The mass just before operation was about one-third of its original size. In the treatment of this case the following factors were used: 200 K. V. pulsating, 4 ma. of tube current, 2 mm. copper and 1 mm. aluminum filter, 50 cm. tube distance, wave length effective 0.12 Å units, quantity 3.5 r per minute, 3 fields of 180 sq. cm. anterior, posterior and lateral, 3000 r to each field, daily dose 200 r to each of 2 fields morning and afternoon, total dose 9000 r."

**CANCER OF LARYNX.**—Carcinoma of the larynx is held responsible for nearly 2 per cent. of the total number of cancer deaths, according to J. C. Beck and M. R. Guttman. Most neoplasms of the larynx are slow in growth and late in metastasizing. About 75 per cent. of them become inoperable if treatment is delayed. Palpable lymph nodes indicate a hopeless condition. A 4-Gm. **radium pack** at a distance of 6 to 15 cm. has effected a disappearance of the carcinoma in several cases, but recurrences have developed in a number of those treated. Coutard's method of x-radiation has been frequently followed by recurrence.

I. S. Hirsch and S. M. Baum (Radiology 24:281 (Mar.) 1935) report a series of 13 cases of proved carcinoma of the larynx treated by **x-rays**. The *technic* used was 180 K. V. constant potential; 4 ma., skin-target distance 60 cm., filter 2 mm. Cu. and 1 mm. Al.

Both left and right sides of neck were treated and 6 treatments a week were given. The total dosage was 5000 to 8600 r, which was sufficient to cause complete exfoliation and destruction of the mucous membrane.

In the 13 cases reported, intrinsic lesions were present in 4 and extrinsic lesions in 9 instances. Five patients are still alive and of these, 2 had intrinsic lesions and 3 extrinsic lesions. Of those who died, recurrences had developed in most cases after 5 to 12 months. One patient had remained comfortable and free from disease for 3 years.

The authors believe that *squamous-cell epithelioma* fully differentiated, non-infiltrating and intrinsic (cordal, glottic or subglottic) can be cured by **x-ray treatment**. **Surgery** can also effect cures, but the operative mortality is about 15 per cent. and there is greater loss of function than with irradiation.

The *prognosis* is usually unfavorable in patients with involvement of glands and other surrounding tissues. In these extrinsic cases x-ray irradiation may prolong life and make the patient more comfortable and may even, in some milder cases, result in clinical cures.

The primary results of **teleradium** treatment in cancer of the larynx and hypopharynx at the Radiological Clinic of the University of Lund, are reported by L. Edling (Radiology 25:267 (Sept.) 1935). The apparatus used for the teleradium treatment contains 2 Gm. of radium. The radium-skin distance is usually 5 cm., and fields of treatment are circular, 5 cm. in diameter. The filter is equivalent to 2 mm. of lead. Most throat tumors are 3.5 to 4.5 cm. beneath the skin. The author treats *intrinsic laryngeal cancer* through 5 portals: 1 in front, 2 directly from the sides, and 2 from the sides more posteriorly. Other parts of the neck are not irradiated, as metastases are un-



common. The total dosage has been 52,000 to 90,000 mg. hr. Lighter doses are given through the anterior portal than through the others, in order to spare the larynx from over irradiation.

In *cancer of the hypopharynx* and *extrinsic cancer of the larynx* in which metastases are common, the author gives irradiation through 7 portals: 1 in front, 2 from each side with one above the other, and 1 from each side more posteriorly. The total skin dosage given is 70,000 to 100,000 mg. hrs. Treatments of 2 hours each are given every day and night, Sundays included, for 16 to 24 days. Most patients stand this intensive treatment very well, but sometimes have general exhaustion, nausea and vomiting. In intrinsic laryngeal cancer the results seem to compare favorably with those of surgery in getting rid of the cancerous tissue. The teleradium treatment is far superior to surgery from the patient's standpoint of lack of mutilation and preservation of function.

The teleradium therapy is superior to other methods of radium application in getting rid of metastases. The teleradium therapy is superior to surgery in cases of hypopharyngeal tumor, for surgery causes severe mutilation and only rarely cures the cancer. Teleradium therapy appears to be superior to x-ray therapy, even when the latter is given by protracted fractional doses.

**CANCER OF RECTUM.**—Inoperable cancer of the rectum was treated successfully in 8 cases by B. F. Schreiner by means of **implants of radon** in addition to **external irradiation**. The favorable results in these cases have definitely established the fact that it is possible to effect healing without colostomy or other surgical intervention. Information accumulated in many years of experience has led Schreiner to believe that as soon as the diagnosis of

rectal carcinoma is made and verified by biopsy, the patient should have a thorough course of **x-ray irradiation** or should be treated externally by **telecurie therapy**.

In discussing *radium burns* of the rectum produced in the course of treatment of cancer of the rectum and hypertrophy of the prostate gland, V. C. David (Ann. Surg. 102:422 (Sept.) 1935) states that in 3 cases of rectal carcinoma, even after radium dosage sufficient to cause necrosis, there was definite evidence of carcinoma in the depths of the ulcer under the necrotic exudate. In 2 additional cases similarly treated, the base of the ulcer showed degenerated cells which were very suggestive of carcinoma. This evidence leads the author to conclude that even when cancer of the rectum is treated so vigorously with radium that destruction of normal rectal mucosa takes place, cure of the carcinoma does not necessarily follow.

**EPITHELIOMA OF SKIN.**—*Cancer of the mouth* should be recognized early by both the patient and his physician. If precancerous lesions are treated thoroughly and skillfully, G. E. Pfahler believes the development of cancer should be prevented. The means are at hand to accomplish this and consist of early and complete destruction of moles, warts, crusts, fissures and chronic ulcers by **electrodesiccation**. Epithelioma of the skin of the *cheek* is usually of the basal cell type. When it is first discovered a biopsy should be done, the lesion eradicated by **electrodesiccation** and followed by **irradiation** in a dosage of 1 to 4 erythemas, either with radium or x-rays. Growths adherent to and involving bone or cartilage, are more resistant than superficial lesions. If the report on the biopsy is *squamous cell carcinoma*, the **neighboring lymphatics** should be carefully irradiated.

Epitheliomas involving the *mucous membrane* are always of the squamous cell type and are serious in character. Large doses of gamma irradiation from radium, or highly filtered high voltage x-rays, should be tried. Where the disease has extended from the cheek into the alveolar process or the inferior dental canal, it will probably be necessary to **resect a part of the lower jaw**. Much knowledge has been accumulated regarding implantation of radium needles, dosage of surface application of radium, telecurietherapy and high voltage x-ray therapy.

**CANCER OF URINARY BLADDER.**—In an evaluation of surgery and irradiation in the treatment of this disease, J. R. Andrews and C. A. W. Uhle (Am. J. Cancer 26:507 (Mar.) 1936) report their results in the treatment of 60 cases of carcinoma of the bladder in which the diagnosis had been confirmed by microscopic examination. The cases were grouped as follows:

|   | Patients |
|---|----------|
| 1. Surgery and x-ray therapy combined .....   | 27       |
| 2. Surgery and radium therapy combined .....  | 5        |
| 3. Surgery alone .....                        | 15       |
| 4. Inoperable, x-ray therapy only ....        | 8        |
| 5. Untreated; end stages of the disease ..... | 5        |

Of these 60 patients, 9 were untraced after leaving the hospital. These are included in the report and are considered as having died in less than one year. In the earlier cases, the factors of the x-ray irradiation were: 200 K. V. P. mechanically rectified, 4 to 15 ma., 50 cm. skin target distance, 0.5 mm. Cu. and 2.0 mm. Al. and in a few instances 2.0 mm. Cu. and 2.0 mm. Al. In the later cases the factors were: 160 K. V. constant potential, 15 ma., 50 cm. skin target distance, 0.5 mm. Cu. and 2.0 mm. Al., the effective wave length was 0.17 Å units, the half-value layer

0.88 mm. Cu. and the output 45 r per minute, measured in air. Three portals averaging 17 by 17 cm. were used, 1 anterior and 2 posterior, to obtain cross-firing on the bladder. The treatments were given in accordance with the saturation principle of Kingery and Pfahler. Series of treatments lasted about 3 weeks and the average dose through each portal was 1000 r during this period. Each patient was given about 2½ series. The second series was started 6 to 8 weeks after the first was completed or as symptoms and cystoscopic findings indicated. The total dosage for each portal was 2400 r. The authors feel that this amount of irradiation was too small in some cases and plan to give larger dosages in the future.

The greatest amount of irradiation given to any patient was 7 series over a period of 1½ years. A total of 8200 r was given to each of 2 or 3 portals. The patient had an extensive and inoperable (Grade III carcinoma and was alive and well 4 years after the diagnosis had been made. Another patient with inoperable disease received 3 series of treatments with a total of 5000 r to each of 4 portals. This patient was alive and well 4 years after the diagnosis was made.

Another patient with an extensive and inoperable adenocarcinoma was alive and well 10 years after the diagnosis had been made. This patient had been given only 2 series of irradiation treatments with a total of 1600 r to each of 2 portals.

A summary of the results obtained is given in TABLE I in which special attention is called to Group B treated by surgery alone and Group C treated by combined surgery and x-ray therapy.

It will be noted that of the 27 patients treated by surgery plus x-ray, 6 lived 5 years, a survival rate of 22 per cent. Of the 15 patients treated by surgery

TABLE I  
*Group Survivals*

| Survival Period       | Group A<br>Entire Group | Group B<br>Surgery Only | Group C<br>Combined Surgery<br>and Irradiation |
|-----------------------|-------------------------|-------------------------|--|
| Total . . . . .       | 60 (100 per cent.)      | 15 (100 per cent.)      | 27 (100 per cent.)                             |
| One year . . . . .    | 32 ( 53 per cent.)      | 7 ( 47 per cent.)       | 21 ( 78 per cent.)                             |
| Three years . . . . . | 16 ( 27 per cent.)      | 3 ( 20 per cent.)       | 11 ( 41 per cent.)                             |
| Five years . . . . .  | 9 ( 15 per cent.)       | 1 ( 7 per cent.)        | 6 ( 22 per cent.)                              |

alone, only 1 lived 5 years, a survival rate of 7 per cent. The authors submit the following conclusions regarding the future management of cases of carcinoma of the bladder:

1. *Cystoscopy* should be correlated with *pneumocystography* or *contrast-cystography*.

2. *Biopsy* specimen should be obtained if possible.

3. All patients in whom a diagnosis of carcinoma of the bladder has been made should *first* have a course of **irradiation**.

4. After sufficient time interval has elapsed to allow the normal tissues to recover from the radiation effects, but before the neoplasm has resumed active growth, **radical surgery** should be employed. This time interval is about 6 weeks. It is believed that in cases in which the lesion is anything more than a small pedunculated carcinoma, nothing short of an open operation can be adequate. If facilities are available, **radon seeds**, gold filtered and of small radon content, should be implanted.

5. The course of external **x-ray irradiation** should be repeated **after convalescence**.

6. **External irradiation**, in patients who are *inoperable*, frequently proves of great palliative value in controlling bladder distress and hemorrhage.

7. An efficient follow-up system is indispensable.

CANCER OF UTERUS.—The treatment of carcinoma of the *fundus* of the uterus is attended by two great difficulties, according to Bowing and Fricke: (1) The primary lesion is hidden where determination of its extent in width and depth is uncertain; (2) secondary infection is always present, often with ulceration and necrosis.

Carcinoma of the fundus is relatively slow to spread by extension or metastasis. These factors make **surgery** the method of choice in *operable cases*. When the lesion has spread *beyond the stage of operability*, or when the patient's general condition makes her a *poor surgical risk* then **radium** treatment should be instituted. It offers the probability of palliation and the possibility of a cure. Often the radium treatment will reduce the lesion so that subsequent surgery can be more conservative. For carcinomas of high grade of malignancy, **postoperative irradiation** with **x-rays** or **radium** is of value in reducing recurrences.

Cases are classified by Bowing and Fricke in 4 stages, according to the general condition of the patient and the extent of the growth of the lesions. The method of treatment is based upon the principle of intensive broken doses rather than massive doses. This produces gentler and more gradual reaction in the tissues and less systemic reaction. Moreover, it can be stopped at the first

appearance of complications that contraindicate further irradiation at that time. Simple applicators, which are gamma ray tubes containing 50 mc. of radon, are the unit of treatment. The purpose is adequate homogeneous irradiation of the uterine canal, including the cervix when involved, supported by vaginal irradiation. Radium element needles are employed in cases of *metastasis to the vaginal wall*. Surface packs are used if the *inguinal lymph nodes* are involved. Treatments with x-rays are given following the course of radium treatments, especially in inoperable cases and in those in which the lesions are of a high grade of malignancy.

W. E. Costolow (Radiology 26:193 (Feb.) 1936) reports results in 1143 cases treated by Soiland, Meland and himself between the years 1921 and 1934. Early cases of carcinoma of the cervix and uterus were rare in this series. The Schmitz classification was used in grouping the cases.

Group I.—The clearly localized carcinoma; beginning nodule.

Group II.—The doubtfully localized carcinoma; beginning ulceration.

Group III.—The invading carcinoma, parametrial involvement.

Group IV.—The terminal carcinoma; (a) fixation; (b) involvement of adjacent organs; (c) distant metastasis.

In Costolow's series there were 718 cases of primary carcinoma of the cervix, 5 per cent. of which were in group I, 24 per cent. in group II, and 71 per cent. in group III and group IV.

There were 183 cases of carcinoma of the cervix which had previously been treated by surgery and of these, 81 per cent. had definite evidence of recurrence when they came in for treatment by irradiation.

There were 105 cases of primary carcinoma of the *fundus* and 68 cases of

carcinoma of the fundus which had previously been treated surgically. The remaining 69 cases were carcinomas occurring in the *cervical stump* following previous subtotal hysterectomy.

Costolow remarks that the irradiation treatment which he administered in the early period would be considered inadequate at the present time. The filtration in the radium therapy was never more than 1 mm. of brass, consequently the radium dosage was only about one-half that which is generally applied today.

*Ten-Year Survivals.*—In primary carcinoma of the cervix cases, seen before 1925, there are 15 patients known to be living and free from disease at the present time. Of the total of 209 cases seen, this is a 10-year survival of 7.1 per cent. Some patients died of causes other than cancer; other cases are untraced; and some of the cases were not given irradiation treatment. The survival of this number of cases gives definite proof of the value of even a limited amount of irradiation.

In *postoperative carcinoma of the cervix*, 6 of 90 cases have remained well after 10 years. In *carcinoma of the cervical stump*, 4 of 21 cases have remained well after 10 years.

*Five-Year Survivals.*—In the period from 1926 to 1930, the amount of primary regression, palliation and the percentages of cures increased. Larger doses of radium with heavier filtration were given. Also, x-ray treatments were given in a systematized method with a 200 K. V. P. machine.

In *primary carcinoma of the cervix*, there is a 5-year survival of 58 cases out of a total of 298 cases seen. This total includes cases not treated and others untraced. This is a 5-year survival of 19.5 per cent.

Costolow discusses the progressive stages of earlier irradiation treatments

and then gives the following detailed account of his present method:

*Present Technic.*—Since 1933 in our present technic, a voltage of around a half-million is used with the Lauritsen type tube—distance 52 cm.; filter 0.6 mm. lead (equivalent 12 mm. or  $\frac{1}{2}$  inch copper); effective wave length 0.05 Angstrom; half value layer 0.5 mm. lead; in aluminum, half value layer 23 mm.; depth dose 53 per cent. at 10 cm. (in paraffin). Treatment rate is 15 r per minute. Four or 6 pelvic portals are used; two 15 by 15 cm. portals anteriorly over the pelvis; two 15 by 15 portals posteriorly, and 2 laterally, if 6 portals are used. Daily, 2 portals receive 150 r units (measured in air); total dosage from 1600 to 2000 r is given each portal. This produces a definite erythema with desquamation. Diarrhea is complained of in many cases but usually soon disappears if the daily dosage is decreased. In some cases 300 r is given daily, alternating the 4 or 6 portals. With safety, from 10,000 to 12,000 r units may be given over a period of from 5 to 6 weeks. The plan of this treatment should be individualized considerably, according to the size of the patients and their ability to withstand the irradiation.

The primary growth is markedly influenced by the x-ray series. Often, a cauliflower primary growth of a high degree of malignancy will completely disappear after such a series.

Following the x-ray series, radium applications are commenced immediately, a divided series of vaginal and intrauterine applications being given. In the vaginal application, 2 mm. of gold and 1 mm. of aluminum filter is used, and in the intrauterine application, 1 mm. of gold and 1 mm. of aluminum is used. Previously, we applied a vaginal dosage of from 1200 to 1400 mg.-hrs. and an intrauterine dosage of from 900 to 1200 mg.-hrs. This was repeated in 1 week and again in 2 weeks. Since the supervoltage x-rays have been used, we have reduced the vaginal vault dosage, but have not eliminated it. Usually, however, most of the radium dosage is given intrauterine. With 1 mm. gold filter, a dosage of from 4000 to 6000 mg.-hrs. may be given. This dosage is divided into 1- and 2-week intervals. Many cases which have had the full radium dosage have not shown any bad effects following this heavy irradiation. The fact that the radium follows immediately after the x-ray series is probably the important factor in preventing unduly delayed reactions, because the

tissues in the vaginal vault and cervix have not had time to develop fibrosis and interference with the local circulation, which occurs from 4 to 6 weeks following intensive irradiation.

Certainly, the intrauterine radium can do no harm to the bladder or rectum, as distance and filtration prevent much irradiation outside of the walls of the uterus. We believe the radium dosage absolutely essential in order to give sufficient irradiation to the uterine canal and cervical glands.

*SARCOMA OF SOFT PARTS.*—Irradiation has given better results than any other form of treatment in cases of *lymphosarcoma*, *Hodgkin's disease* and *leukemia*, according to T. Leucutia.

Acute leukemia is apparently not influenced at all by irradiation and few cases survive as long as 9 months. In *chronic* forms of *leukemia*, *lymphatic* and *myelogenous*, duration of life is influenced very little, if any, by irradiation, but the symptomatic improvement of the patient during the few years of survival is remarkable. In cases of *lymphosarcoma* some radiologists have not found that **radium** and **x-rays** prolong life, but T. Leucutia in summarizing the results in several large institutions believes irradiation has definitely prolonged life.

In *Hodgkin's disease* the statistics seemed to show less prolongation of life than in cases of lymphosarcoma, but still there was some prolongation. If the lesions are confined to a small area, the *prognosis* is better than when the lesions are more widespread.

Leucutia used high voltage **x-rays** ranging from 160 K. V. to 200 K. V. He believes that treatment with voltages above 200 K. V. has little promise of results much better than those already reported, except in certain cases of localized lymphosarcoma, where a higher penetration is needed.

Sarcomas vary from one extreme to the other in regard to their sensitivity

to irradiation. On one extreme is the highly radiosensitive *lymphosarcoma* and at the other extreme the highly radioresistant sclerosing *osteosarcoma*. T. Leucutia (Radiology 25:403 (Oct.) 1935) discusses the various types and subtypes of sarcomas with respect to their radiosensitivity, which is the basis for the dosage used in the treatment. The clinical course usually followed by the various types of sarcomas (extension, metastases, etc.) is one of the guides used in determining the fractionation of dosage, intervals between treatments, and duration of treatment. The author reports that in 222 cases of sarcoma treated at Harper Hospital, Detroit, between the years 1922 and 1929, the incidence of survival for 5 to 12 years was 30 per cent. Of the 222 cases, 101 had sarcomas of soft tissues and among these the 5- to 12-year survival was 40 per cent. These soft part sarcomas were grouped as follows:

1. Fibroblastic sarcoma.
2. Fibrosarcoma.
3. Neurosarcoma.
4. Myxosarcoma.
5. Leiomyosarcoma.
6. Rhabdomyosarcoma.

The cases are tabulated with regard to age, sex, histological diagnosis, origin, stage, type of treatment, dose, series, extent of treatment, extent of metastases result, duration since onset, and duration since treatment.

The technic of x-ray treatment was 200 K. V., 1 or 1.5 mm. Cu. plus 1 mm. Al. filtration, making the effective wave length 0.13 to 0.14 Angstrom units; 30 to 100 per cent. of a skin unit dose was given to each portal. This was varied according to the estimated radiosensitivity of the sarcoma.

The *fibroblastic sarcoma* group consisted of 61 cases and the 5- to 12-year survival rate was 21 per cent. In it are included all the sarcomas which do not

belong to other well-defined groups by reason of distinguishing characteristics. The sarcomas in this group presented the greatest variation in radiosensitivity. In a general way their morphological structure, degree of differentiation of cells, vascularity of the tumor, and amount of paraplasmic structure determined the response of the sarcoma to irradiation. Most of the tumors were quite bulky and the irradiation was rather heavy, from 90 to 100 per cent. of a skin unit dose. In many cases, surgery was used in addition to the radiation therapy. Supplemental irradiation was given to regions known to be favorite sites for metastases of the sarcomatous tissue under treatment.

*Fibrosarcoma* and *neurosarcoma* have many characteristics in common, especially in regard to histogenesis and radiosensitivity. **Radical excision** was done in 17 cases of fibrosarcoma reported by Leucutia and this was followed by *postoperative* prophylactic **irradiation**. Of the 17 cases, 82.4 per cent. survived the 5- to 12-year period.

In the series reported there were only 3 cases of *neurosarcoma*. One patient has died and the other two have remained alive for 7 years. One of these patients has had radiation therapy throughout the 7 years, consisting of 30 series of treatments. The lesion at the end of that time was smaller than at the beginning of the treatment, but had not entirely disappeared. Leucutia remarks that in rare instances, malignant tumors of nerve trunks may be very radiosensitive, as for example, a case reported by Stewart in which a ganglionic neuroblastoma, probably arising in the cervical sympathetic ganglion, seemed to be as radiosensitive as lymphosarcoma. Later, metastases developed in the lungs, but regressed dramatically to irradiation. They developed a second time and regressed a second time to

irradiation. The patient, a young boy, finally died when he could not tolerate further irradiation.

*Myxosarcomas* develop slowly and often reach a large size before causing discomfort to their hosts. Metastases to regional lymph nodes and lungs are a very late complication. These tumors respond well to irradiation if given in large dosage, 90 to 100 per cent. of a skin unit dose. Several series of treatments may be required to cause complete disappearance of the sarcoma, as regression is much slower than in some other forms. In the 8 cases reported, 4 (50 per cent.) have apparently been cured. In the cases which died, metastases developed in the lungs, in 1 case nearly 4 years after complete disappearance of the primary tumor.

The pathologic criteria of *leiomyosarcoma* are ill-defined. Some investigators claim that the condition occurs rather frequently, while others have observed it only rarely. The chief difficulty in the histologic diagnosis of myoma and myosarcoma lies in the variation of opinion as to the exact proportion of the embryonal and adult elements necessary for the classification. The author quotes Ewing as stating that benign myomas may vary in structure in different portions and probably at different periods, but these changes constitute only a local and temporary acceleration of growth, without evidence that they will be transformed into malignant sarcomatous degeneration. It is well known that the radiosensitivity is low in myomas that show degeneration, whether malignant or otherwise, and degeneration calls for **surgical intervention with postoperative irradiation.**

In the 8 cases of leiomyosarcoma reported by Leucutia, 7 originated from the uterus and 1 from the aortic wall. They were treated with heavy irradiation,

90 to 100 per cent. of a skin unit dose, following **surgical operation.** In a few cases, moderate palliation with temporary restraint in growth of the tumor resulted, but only 1 patient of the 8 remained well for a period of 5 years.

In *rhabdomyosarcoma*, the criteria of radiosensitivity are nearly identical with those of leiomyosarcoma and consequently the radiation results are equally unsatisfactory. Of 3 cases of rhabdomyosarcoma (2 of the kidney and 1 of the thigh), treated by the writer, none survived 1 year following irradiation. Leucutia sums up his work with the following conclusions:

"In reviewing the statistical results in relation to the therapeutic method used in this very complex group of sarcoma of the soft parts, it becomes apparent that neither surgery nor radiation therapy has hard and fast rules. As concerns the former, though the general principle may be that every operable sarcoma should be removed at once, there are instances in which primary radiation therapy may appear of greater benefit. Especially is this true of some highly cellular sarcomas of the fibroblastic group, such as round-cell sarcoma of the tonsil or any other location, reticulum-cell sarcoma, large spindle-cell sarcoma, etc., of the myxo-, lipo-, and xanthosarcomas and of the Kaposi sarcoma of the skin. Moreover, when biopsy is taken in all these instances, it appears considerably safer to attempt to remove a metastatic node *in toto*, rather than try to cut into the tumor proper. As concerns radiation therapy, the degree of radiosensitivity forms the basis of procedure. Yet radiosensitivity in the clinical sense may mean 'spectacular' regression in one case and slow progressive tumor shrinkage in another. The criteria dominating such response must be closely scrutin-

ized and classified. It will be found that in the majority of cases they may be harmonized to greater advantage with surgical indications and that, therefore, an association of surgical and radiotherapeutic methods in the treatment of sarcoma of the soft parts must constitute an essential and most desirable requirement. In the same sense, statistics dealing with a combination of the two methods rather than their opposition will prove of the greater clinical value."

**Polycythemia Vera.**—"Spray x-ray therapy" is used for the treatment of the whole body at once. It is also called "teleroentgenotherapy," "roentgen baths," or "total irradiation." The technic used by F. T. Hunter (New England J. Med. 214:1123 (June 4) 1936) at the Massachusetts General Hospital was 200 K. V. P., 4 ma., filter 0.5 mm. Cu. and 4 mm. celluloid, 215 cm. skin-target distance. The rate of irradiation was 20 r per hour (measured in air). In theory, the method of treating radiosensitive widespread lesions as a whole, not piecemeal, seems quite feasible. Several radiologists have employed it in cases of *leukemia* and *lymphoblastoma*, but their results have not been uniform in demonstrating its usefulness. In radioresistant neoplasms the "spray x-ray therapy" has not proved as effective as more intense irradiation through medium or small-sized portals. A few cases of *polycythemia vera* have been treated by the "spray x-ray therapy" and reports in the foreign literature have been mildly enthusiastic. As these reports have not appeared in the English literature, the author believes it will be of interest to present 2 personal cases which were treated and followed closely for 3 years.

The first patient was a white woman who developed thromboses in the superficial veins of the thighs, with edema of the femoral regions and sharp pains in the chest which

were thought to be due to pleurisy. The thromboses became more numerous and one of them appeared on the right lower abdomen. This one was 12 cm. in diameter, red, slightly tender and indurated. The jugular veins could be palpated as hard cords on both sides of the neck. The retinal vessels were distended and tortuous and there were many hemorrhages into the retinae. The blood showed 8,500,000 red blood corpuscles, hemoglobin 125 per cent. (Sahli), 12,000 white cells. There were 85 per cent. polymorphonuclears. The x-ray treatment given to this case is reported by the author as follows:

"Spray therapy was begun November 11th and was continued through December 7, 1932. The apparatus was operated so as to deliver to the patient about 20 r per hour (measured in air) at a target skin distance of 215 cm., through 0.5 mm. of copper and 4.0 mm. of celluloid; M. A. 4, K. V. P. 200. A total of 304 r was given in 11 sittings. A second course of treatment (with the same arrangement of the apparatus) was begun on January 24, 1933, and completed on February 28, 1933. In this course of therapy 598 r were administered in 26 sittings. Thus, a total of 902 r was received by the patient in about 10 weeks time." The author has published a curve showing the blood count for 3 years. The red cells dropped to 4,000,000 soon after the completion of the second series of treatments and gradually rose again, but has not reached the 6,000,000 level. The patient appeared normal in every way at her examination in the early part of this year.

The second patient was a 52-year-old white man who, on March 8, 1933, had 10,630,000 red blood corpuscles per cu. mm.; hemoglobin 125 per cent. (Sahli); polymorphonuclears 85 per cent. Red blood cells were normal in appearance. The x-ray treatment was as follows:

"Spray therapy was given between June 6th and July 20, 1933; but it was subsequently discovered that because of difficulties encountered in computing dosage, the patient had received, during this period, only a fraction of the prescribed amount of therapy. (Note that the erythrocyte count did not fall during this time.) A new course of therapy was begun on September 25th and completed on October 25, 1933, the patient receiving a total of 1192 r in 22 sittings. The apparatus was arranged as in case 1 except that an increase of the milliamperage to 6 raised its output to approximately 54 r per hour. An additional small amount of therapy, totaling 180 r was administered between July 22 and July 29, 1935,



in 6 sittings." Soon after the spray therapy in 1933, the red blood count dropped to 5,000,000. It has gradually risen so that it was slightly over 6,000,000 in the early part of this year. All the symptoms of polycythemia vera have disappeared, and the patient feels perfectly well.

In commenting on these 2 cases of polycythemia vera, the author makes the following statement.

"From the previously reported cases of polycythemia vera treated by the 'spray therapy' and from the 2 records here, it can be stated that this type of irradiation is definitely superior to the therapeutic agents in common use. Roentgenotherapy through small fields has not demonstrated its practicability as a routine measure. Dangerous drugs, such as phenylhydrazine and arsenic, require constant supervision and cautious administration, even then they often give rise to gastrointestinal disturbances, jaundice, or skin eruptions. Phlebotomy, an unpleasant procedure at best, not only must be performed at frequent intervals, but on occasion is ineffective. And as for daily stomach washes which have been recently suggested, one can only agree with Publius Syrus: 'There are some remedies worse than the disease.' 'Spray therapy,' on the other hand, when administered in small doses over long periods of time, has an astonishingly prolonged depressant effect on the blood forming organs, produces no disturbing clinical symptoms, and may be given without interruption of the patient's daily work. For these reasons, therefore, I believe it to be the treatment of choice in polycythemia vera."

#### ***Erythroblastic Anemia (Cooley).***

—Hereditary erythroblastic anemia (Cooley), a pathologic entity manifesting itself in certain infants of Mediterranean parentage, has some histologic points in common with polycythemia vera. Within the knowledge of F. T.

Hunter (*Ibid.*) this disease had never been treated by the "spray therapy" previous to the fall of 1935, when treatment of the case, which he has reported, was begun. Erythroblastic anemia (Cooley) had been treated unsuccessfully by x-rays through limited portals.

The patient was a 7-year-old boy, American-born of Italian parentage. At the time of entrance into the hospital, September 5, 1935, he was pale and sallow and could not climb a flight of stairs without becoming tired out. Two sisters of the patient also have hereditary erythroblastic anemia.

The patient had 2,540,000 red blood cells per cu. mm., hemoglobin 28 per cent. (Sahli), polymorphonuclears 56 per cent., lymphocytes 25 per cent., normoblasts 15 per cent., hematoblasts 2 per cent., unclassified cells 2 per cent. The erythrocytes exhibited extreme variation in size and shape with many tailed forms, microcytes, macrocytes, stippled and polychromatophilic cells. The platelets were somewhat decreased in number.

The treatment was as follows: "Spray therapy was begun on September 10th and complete on September 25, 1935, a total of 360 r being given in 14 sittings. The apparatus was that used in the treatment of the first two patients but so arranged that approximately 40 r per hour (measured in air) was received by the patient."

As this was the first case of its kind ever treated by the "spray method," it was not known in advance just how large a dosage should be used. Unfortunately, too much treatment was given and an acute bone-marrow depression resulted. The white cells of the blood fell to 500 per cu. mm. and the platelets almost disappeared. This crisis was accompanied by *purpura* and alarming *epistaxis*. A series of **blood transfusions** was given. Conditions improved after that and in the course of a month the number of white cells reached normal and the red count came up to about 4,000,000, with a reduction in the number of nucleated red cells in the circulating blood. The subjective symptoms disappeared and the child, though still somewhat pale, became bright and active and can play with children his age without getting tired out. He has gained in weight and is able to go to school.

In commenting on this case, the author makes the following statement:

"This single case of erythroblastic anemia treated with the 'spray therapy' neither invites lengthy discussion nor warrants generalizations. It does demonstrate, however, that irradiation by this method has a rather marked depressant action on rapidly proliferating erythroblasts in the bone-marrow; and that, with the consequent lowered rate of hematopoiesis, fewer immature cells appear in the peripheral blood, an increased number of erythrocytes reach the blood stream and a definite clinical improvement takes place in the patient. It is, of course, too early to comment on the lasting effects of the treatment, or on the frequency with which it should be repeated. Obviously, the dosage used in this case was administered at too rapid a rate. Doses from 10 to 20 r given at 5-day intervals, might possibly produce beneficial results without such a marked effect on the leukoblasts and megakaryocytes. However that may be, the result of 'spray therapy' in one case of erythroblastic anemia is presented here with the hope that further observations will be made."

**Acute and Chronic Inflammatory Conditions.** — Inflammatory conditions require comparatively small doses of x-ray irradiation for their cure, according to A. U. Desjardins (Texas State J. Med. 31: 616 (Feb.) 1936). This is in contrast to neoplastic conditions which, in general, require large doses. Inflammatory conditions may be treated by competent radiologists with little danger of deleterious effects from the irradiation itself.

Many forms of acute inflammation are cured promptly by a single small dose of x-rays. The more acute the infection, the smaller the dosage required to cure it, and the earlier in the disease treatment is started, the more likely are results to be favorable, *i. e.*, prompt relief of pain and subsidence of congestion, red-

ness and temperature. In some cases, relief of pain may be preceded by a moderate increase for a short time after the irradiation. Good results are more likely if irradiation treatment is started during the stage of leukocytic infiltration rather than in the later stage of suppuration.

Polymorphonuclear cells, lymphocytes and eosinophiles play an important part in the defense mechanism against infection. These cells are sensitive to x-rays and it appears that some of these defense cells must be destroyed by the irradiation. At first thought, this might appear to be the exact opposite of the result desired, but an explanation may be that antitoxins, bacteriolysins and other protective substances are liberated suddenly when some of the defense cells are disintegrated. In this way, the antibodies are made available more quickly than when they must be utilized by natural processes involving the intact cells. Leukocytic infiltration is favorable for successful irradiation therapy, but the presence of connective tissue around the inflammatory lesion is unfavorable. In other words, when a process is chronic and fibrosis has taken place, larger doses of x-rays are required for favorable therapeutic results.

*Furuncle, carbuncle, cellulitis, phlegmon, onychia, paronychia, abscess, acute adenitis, erysipelas and gas-bacillus infection* are usually considered to be in the group of acute inflammatory lesions which are favorably affected by irradiation.

"Certain other acute inflammations such as sinusitis, mastoiditis, pelvic infection, and osteomyelitis also seem to be influenced favorably, but the accumulated evidence is not yet absolutely conclusive. The incidence of favorable results runs fairly consistently between 70 and 80 per cent. The fact that many patients recover promptly without opera-

tion does not mean that irradiation should supplant surgical measures. Rather, the surgeon and radiologist should coöperate all the more closely because, even when irradiation has had a good effect, the shortening of the inflammatory process may require a more prompt, if less extensive, intervention.

"According to A. J. and W. A. Quimby, 'no pathological process in the body responds quicker to an x-ray exposure than the nonresolution following pneumonia.' Other reports have tended to confirm this view. An equally favorable effect of irradiation in a large percentage of cases of postoperative pneumonia as well as cases of pneumonia unrelated to surgical intervention has been recorded."

*Erysipelas* often responds very promptly to a moderate dose of **x-rays**, the fever diminishing in 12 to 36 hours. In many cases the disease continues to recede after one treatment but in some cases the remission is temporary and additional x-ray treatments may be required. The area irradiated should be more extensive than the visible inflammation. **Ultraviolet radiation** may be used instead of x-ray radiation in the treatment of *erysipelas*, but the dose required is great enough to cause a heavy erythema and blistering. This obscures the extent of the *erysipelas*, making it difficult to determine whether the disease is receding or extending.

*Acute parotitis* is a complication of severe surgical operations which is rather uncommon but is very serious when it does occur, carrying a mortality rate of 35 to 60 per cent. when treated by the usual methods. According to some authorities, it occurs 15 to 20 times as often after operations on the colon as after any other operations. While the parotitis is in the early infiltrative stage it may be treated with moderate doses of **radium**. The inflammation will

often subside in 24 to 48 hours and suppuration will be prevented. This is so commonly effective that suppuration occurs in only one-tenth as many cases treated by radium as by other methods. Mortality is reduced the same as suppuration. Radium treatment can be given without disturbing the patient. Except for this factor, it seems probable, from tests on a few cases, that **x-ray** treatment would be as effective as radium treatment.

*Tuberculosis, actinomycosis, trachoma* and *active infectious chronic arthritis* are some of the chronic inflammatory conditions which have been known for a long time to be favorably influenced by **x-ray therapy**. The dosage required in chronic inflammation is larger than that required in the treatment of acute inflammatory conditions and the treatments must be repeated several times at suitable intervals. The dosages used should not be as large as those used in treating tumors and should not cause erythema or reach the limit of tolerance. Tuberculous lesions are affected only slowly by irradiation and in *tuberculous adenitis*, for example, the treatment must be given every 3 or 4 weeks for 3 to 12 months. In the absence of calcification, the inflamed lymph nodes gradually recede and either disappear completely or remain as small fibrous granules. Caseous material may be slowly absorbed or replaced by calcium. When suppuration occurs, the pus is often fluid enough that it may be aspirated through a large bore needle. The best practice is to introduce the needle obliquely through dense tissue rather than directly through the thinnest tissue overlying the area of suppuration. In this way a sinus is less likely to result. In some cases the pus cannot be aspirated and incision is necessary. X-ray treatment in these cases has reduced the size of the abscess so that the incision need not be as

extensive as in similar cases not treated by irradiation.

Ultraviolet irradiation is a valuable supplement to the x-ray irradiation, and seems to hasten resolution of tuberculous lesions. It should be given to the whole body in daily increasing doses. Ultraviolet treatment of the affected parts only, does not seem to have any value.

*Tuberculosis of the peritoneum* is benefited by x-ray therapy in much the same way as tuberculous adenitis. *Tubercles in the cornea and iris* recede more rapidly after exposure to x-rays than tuberculous lesions in any other part of the body. In irradiating the eye, the dose of x-rays should not exceed three-fourths of an erythema dose. Larger doses, especially in the cases of children, might lead to cataract and epithelial degeneration in the lens.

*Trachoma* can sometimes be cured by x-ray therapy. The early stages of the granular form of the disease are more easily cured than are the later stages when granulations have been replaced by connective tissue. In many cases, even though the disease may not be completely cured, it shows improvement under irradiation.

*Chronic infectious arthritis* treated by x-rays shows favorable results in a large enough percentage of cases to warrant consideration of this method of treatment. The improvement varies in different cases in regard to the relief of pain, reduction in swelling, and reduction in functional disability. Focal infection should be eliminated, if possible. As in other forms of inflammatory disease, the quickest and best results are obtained when treatment is begun early, while the inflammation is active. When treatment is not begun until the disease is in late and chronic stages, a greater number of treatments must be given.

*Actinomycosis of the face, mouth* and other superficial tissues can be cured

in a large proportion of cases by x-ray irradiation supplemented by large doses of iodides internally. In some cases incision of the abscess to effect drainage is necessary also. When the actinomycotic infection involves the *intestines* the proper treatment is x-ray irradiation of the entire abdomen, front and back. Moderate dosage is used and treatments are repeated several times at intervals of 4 weeks. Exploratory operation is contraindicated, as it tends to spread the infection. In some cases localized abscesses may be drained by simple surgical incision to advantage. When actinomycotic infection involves the lungs any form of treatment is not likely to produce more than slight and temporary improvement.

*Acute Postoperative Parotitis.*—In discussing this complication, J. M. Robinson and J. Spencer (New England J. Med. 215: 150 (July 23) 1936) state that infection of the parotid gland, either unilateral or bilateral, is a serious complication which may follow almost any variety of severe surgical operation. It seems to be more likely to complicate resection of the colon than any other operation. In general, however, it may be said that the more debilitated the patient and the more severe the operation, the more likely is the occurrence of infection of the parotid gland. *Predisposing factors* are general dehydration, hyperpyrexia, restriction of fluid intake by mouth, and lack of flow of saliva following administration of opiates and atropine.

Acute postoperative parotitis has been recognized as a serious complication for some time. The usual method of treatment has consisted of the application of hot or cold compresses to the swelling and then incision as soon as fluctuation can be recognized. Combined American statistics reported by Green gave a mortality of 58 per cent. for this method

of treatment. In commenting on it, the author says: "It is true that at least a third of these deaths can be ascribed to causes other than the parotitis. In the remaining cases, however, the complication appears to be not merely a terminal event, but is apparently the immediate cause of death, usually representing the final blow to already weakened recuperative powers."

Bowing and Fricke, of the Mayo Clinic, have reported the results in 183 cases of acute postoperative parotitis treated in that institution by means of radium. The technic employed was 2, 3, or 4 units of 50 mc. of radon, or equivalent amounts of radium mounted upon wooden blocks 3 cm. square, to make the skin-distance 2.5 cm., with filtration of 0.5 mm. silver and 1 mm. brass and 2 mm. lead. Treatments lasted 8 hours and were given 1 to 4 times, depending upon the response. In the case of an infected region too large to be covered by 4 blocks, 4 more blocks were used after the initial treatment, to cover the additional area. These rather large amounts of radium could not be replaced by smaller amounts applied nearer the skin, because a dangerous skin dosage might then be given, with an ineffectual amount of radiation penetrating to the depths of the infected gland. Filtration could not be reduced without endangering the skin.

Bowing and Fricke report a death rate following the radium treatment of 22.8 per cent., but the parotitis was the immediate cause of death in only 6 per cent., the remaining 16.8 per cent. dying of some other complication, the original disease, or the effects of the operation. If all the deaths, 22.8 per cent., are considered as failures of therapy, the results will compare favorably with a series of cases treated with compresses and surgical drainage at the Mayo Clinic in which the mortality was

39 per cent., as reported by Rankin and Palmer.

At the Massachusetts General Hospital, high voltage x-rays have been used instead of radium in the treatment of acute postoperative parotitis and Robinson and Spencer (*Ibid.*) report the results obtained.

X-rays have some practical advantages over radium, one of the most obvious being that the treatment can be given in minutes instead of hours. One of the disadvantages is that the patient must be moved to the x-ray department, except in hospitals where mobile x-ray apparatus is available. The technic used was, 200 K. V. P., 50 and 60 cm. skin-target distances, 0.5 mm. Cu. and 1 mm. Al filters, effective wave length 0.16 Angstrom units. Through a 19 cm. cone 300 r (occasionally 200 and 400 r), measured in air, were given at one sitting to the involved parotid gland. In cases of bilateral infection, both sides were treated at the one sitting. This dosage is approximately one-half of a skin erythema dose.

In the series of 12 cases here reported, 3 patients died, making a mortality rate of 25 per cent., which compares favorably with the 22.8 per cent. mortality rate, reported by Bowing and Fricke, following the use of radium. The authors point out that the x-ray treatment should be given as early as possible in the course of the inflammation, in order to abort the suppuration which is so common in parotitis. Early treatment may abolish the pain associated with swelling of the parotid in the same manner as similar treatment may abolish the pain associated with a carbuncle.

Robinson and Spencer (*Ibid.*) were especially pleased with the results obtained in 4 patients with *bilateral parotitis*. All these patients recovered in spite of the fact that bilateral infec-

tion is usually more serious and carries a higher mortality rate than unilateral infection.

The usual course of the disease in their patients was as follows:

"Two days to two weeks after operation there was a sharp rise in pulse and temperature. Soon after, the patient complained of pain at the angle of the jaw and trismus. A swelling below and in front of the ear appeared, rapidly increasing in size. Cloudy or frankly purulent secretion could sometimes be expressed from the reddened papilla.

Generally within 4 to 24 hours after the swelling was noted, roentgen treatment was given. The infection then took one of three courses:

1. Within 12 hours of the treatment, the swelling and pain had increased markedly. In the following 24 hours both began to subside. At the end of 3 days to a week later, there was little or no residual evidence of inflammation.

2. Within 6 to 12 hours, the pain had markedly decreased although the gland did not change in size. Twenty-four to 48 hours later, however, it was definitely smaller, and improvement continued as in the first group.

3. There was no response to therapy for 48 hours, after which the fever, pain and swelling diminished very slowly.

The early disappearance of the pain and discomfort associated with the swelling was particularly striking in some of the cases observed. When the response was slow, the temptation to excise the mass was great. Delay was usually rewarded; the swelling eventually subsided without abscess formation or else became localized so that only a small incision was necessary."

**Skin Diseases.** — X-ray therapy is considered by A. M. H. Gray to be one of the most valuable means of treating skin diseases, but it has its *dangers* as well as its advantages. A single small dose of x-rays applied to delicate normal skin, as, for example, on the forearm, produces no visible effect. If this is repeated several times, or if the dose of a single treatment be raised to a certain threshold value, there may appear a redness after about a week. This may last 3 or 4 weeks and

then be followed by pigmentation lasting for several weeks more. When larger doses are applied, the erythema appears earlier and lasts a longer time. The larger the dosage, the more likely are additional effects, such as edema, vesication, ulceration and pain. Even after healing has occurred, there may be an atrophic scar, devoid of hair and sweat glands, and disfigured by irregular patches of pigmentation and telangiectasis. Even small doses repeated many times may cause this atrophy and scarring of the skin. It may take many years for these changes to develop. A certain threshold dose of x-rays applied to the scalp may cause the hair to fall out in the treated area. If this epilation dose has not been exceeded, the hair will grow in again, so that in the course of a few months it will have entirely regrown. If, however, this threshold epilation dose has been exceeded, the hair may never grow in again.

The *treatment of hypertrichosis by x-rays* is strongly *condemned*, because in order to remove the hair permanently such large doses are necessary that the skin cells must be injured. Telangiectatic scars are likely to result which cosmetically are far worse than the original hypertrichosis.

Epilation by means of **x-rays** is a valuable help in the treatment of *ringworm of the scalp*. The x-rays do not kill the fungi of ringworm, but bring out the hairs so that the antiparasitic ointment will have a better chance to act. If epilation is attempted for this purpose, it should be carried through to completion. A single epilation dose is given to each of 5 areas.

There are many skin diseases which *respond favorably* to x-ray treatment, or a combination of x-rays and other means according to Gray. Among these

are *eczema*, *eczematous occupational dermatitis*, *chronic eczema of the palms and soles with hyperkeratosis*, *lichenified eczemas of the flexures*, *psoriasis* localized in small areas, *lichen planus* localized in small areas, *acne vulgaris*, *folliculitis of the beard region*, *pruritus ani*, *pruritus vulvæ*, *hyperhidrosis of axillæ*, *hands and feet*, *mycosis fungo-*

*cides*, *warts*, *keloids* and *malignant skin growths*.

There are several conditions that do not respond to x-ray treatment as favorably as would be expected. Among these conditions are *lupus erythematosus*, *exfoliative dermatitis*, *pityriasis ruba pilaris*, *congenital tumors*, *vascular nevi*, *moles*, *linear nevi*, *ichthyosis*, and *hystrix*.

# CLINICAL PATHOLOGY

By ROBERT A. KILDUFFE, A.M., M.D.

Duclaux, the student, associate, and successor of Pasteur as Director of the Pasteur Institute, once wrote: "Medicine is a strange terrain. It is an edifice where nothing remains standing. . . . Who knows? Perhaps a section of wall will blow up somewhere and a little light will penetrate through the opening thus made."

As even the casual reader of medical literature can attest, these words are as true today as when they were written many years ago, and will still be true tomorrow; for the medicine of the future arises from the medical literature of today, and each day, almost, sees some change, some advance in this field or that. And so constant is this flux and flow, that it is often a matter of difficulty to select from all that is available the contributions of greatest value or those marking a permanent advance.

**THE BLOOD.—CYTOLOGICAL STUDIES.**—Among the more recent investigations is that of P. D. Rosahn and A. E. Casey (Am. J. M. Sc. 192:456 (Oct.) 1936), who use the term "*hemacytologic constitution*" to designate the composite blood formula for the individual, race, or family.

From weekly or bi-weekly blood counts upon 5 rabbits over a period of 2 years and upon 6 healthy young men for 1 year, the mean values for each of the blood elements of each individual were calculated and a comparison made of the individuals of each group with regard to these mean values.

In the men, statistically significant values were noted for the red cell count

and total white cell count, and for the neutrophils, basophils, eosinophils and lymphocytes in both absolute and relative numbers, and for the monocytes in absolute numbers.

Among the rabbits, statistically significant values were observed for the hemoglobin in per cent., the red cell count and total white cell count, and in the absolute and relative numbers of neutrophils, basophils, eosinophils, lymphocytes, and monocytes.

Previous studies by A. E. Casey, P. D. Rosahn, C. K. Hu, and L. Pearce (Science 79:189, 1934) had shown that a characteristic and typical blood formula existed for each variety of standard breed of rabbit studied and hence that a hemacytologic constitution existed for races or breeds of rabbits.

The present study offers biometric evidence to support the concept that a hemacytologic constitution exists for individuals as well as for races.

The difficulties attendant upon the clinical interpretation of relatively minor variations in both white and red cell counts have long been appreciated by the clinical pathologist, though not always to an equal degree by the clinician, and it is with reference to such problems that these studies have an immediate and practical application.

That the leukocytes undergo a normal and rhythmic variation in the normal individual within limits different in different persons but constant in the same person, has been recognized since the studies of Doan and other workers as long ago as 1927, while Medlar in 1929 called attention to the fact that the



leukocytic formula for the individual had been previously established.

The conclusion of A. F. B. Shaw (*J. Path. and Bact.* 38:259 (May) 1934), corroborated by W. E. Garrey and W. R. Bryan (*Physiol. Rev.* 15: 597 (Oct.) 1935), that the number of leukocytes is a character of the individual, receives biometric support in the present studies of Rosahn and Casey, whose evidence indicates that healthy individuals differ widely with respect to their blood formula. As these differences were shown not only in rabbits but in healthy young men, it is concluded that they are due to inherent or constitutional variability among individuals and that each individual has a characteristic and typical blood formula, largely determined by genetic factors.

The evidence obtained in these studies further indicates that the blood cell formula which is normal for one individual may in fact be abnormal for another—a matter of some practical significance and importance.

This is well shown by the data pertaining to the individuals studied.

In A, for example, whose mean white cell count plus  $2\frac{1}{2}$  times the standard deviation was 9276 ( $7036 + 2\frac{1}{2} \times 896 = 9276$ ), a total leukocyte count of 9000 would be within normal limits.

In individual B, however, whose mean count plus  $2\frac{1}{2}$  times the standard deviation was 8081 ( $5779 + 2\frac{1}{2} \times 921 = 8081$ ), a total leukocyte count of 9000 would represent a leukocytosis; a neutrophil count of 2000 in B would lie within his normal range ( $3075 - 2\frac{1}{2} \times 483 = 1868$ ), while the same count in C would constitute a leukopenia as falling without his normal range ( $4207 - 2\frac{1}{2} \times 623 = 2650$ ).

Similarly, a red cell count of 3.7 millions for A would lie within that individual's normal range, but in B would

be outside the normal limits for that individual.

It is important to emphasize that the young men subjected to study were all in good health, in the same decade of life, ingesting approximately the same type of food, and living in a nearly uniform physical environment.

While, in the light of present knowledge, the statistical differences observed must be largely a matter of conjecture, the well-known variability of such biologic phenomena as body build, degree of pigment, physical conformation, etc., suggests as a tenable hypothesis that the potential blood cell level of an individual is determined by genetic factors and is as characteristic of that individual as the color of his eyes or his physical type.

While this inherent potentiality is subject, of course, to the conditioning influence of environmental stresses such as disease, the available evidence suggests that it is fundamental and characterizes and typifies the individual.

If this be true, it becomes obvious that minor variations in white and red blood cell counts, as well as minor fluctuations in the distribution of the various white cell elements, may be of value in the detection of early pathologic processes when the numerical variability of the different blood elements have been previously determined in the individual by repeated blood counts during health.

#### BLOOD SEDIMENTATION.—

The clinical significance of variations in the suspension stability of the blood are now rather well defined as an indication of activity without differential value.

Recent studies of blood sedimentation have largely been devoted to attempts to discover and explain its mechanism, or, in other words, to determine the underlying factors responsible for the variations in blood sedimentation which accompany pathologic processes.

Among the more recent of such studies is that of S. P. Lucia, T. Blumberg, J. W. Brown, and S. M. Gospe (Am. J. M. Sc. 192:179 (Aug.) 1936), who conclude from study of 102 cases that sedimentation time is apparently accelerated as globulin content of the serum increases and is retarded as the albumin content of the serum increases.

However, it cannot be hastily concluded from this study that acceleration of the blood sedimentation time depends wholly upon an increase in the serum globulin, for the differences observed, though statistically significant, were low. Moreover, as has been shown by other workers, as well as in this study, decreased erythrocyte counts and increased neutrophil counts are also associated with decreased blood sedimentation rates, although the latter assumption is open to question in that the underlying processes responsible for the increased sedimentation may also be responsible for the neutrophilic leukocytosis.

An extensive study of the various physicochemical factors influencing the red cell sedimentation rate is that of K. Yardumian (Am. J. Clin. Path., in press), covering over 2000 cases, determinations being made by the Linzenmeier method.

Yardumian's results may thus be summarized:

1. Factors without appreciable influence upon the sedimentation rate: (a) Different anticoagulant; (b) variations in standardized technics; (c) variations in temperature (20° C. to 30° C.); (d) remixing and resedimentation; (e) variation in chemical composition of the blood: blood sugar, nonprotein nitrogen, calcium, phosphorus, CO<sub>2</sub> combining power, cholesterol, plasma and cell chlorides, albumin-globulin ratio, and variation in the number of platelets and leukocytes, these last two particulars not being in agreement with the studies

cited above, which, however, include only 102 cases.

2. A moderate effect upon the sedimentation rate is exerted by the following factors: (a) A delay of more than 2 hours in conducting the test decreases the sedimentation rate; (b) extreme variation in temperature, below 20° C. producing a decrease and above 30° C. producing an increase in the sedimentation rate; (c) marked variations in the albumin-globulin ratio increase the rate; (d) variations in the length and bore of the sedimentation tube; and (e) marked hyperglycemia (over 200 mgms. per cent.), which slows the rate.

3. Factors producing a marked effect upon the sedimentation rate: (a) High fibrin content (rate accelerated); (b) high total lipoids (rate accelerated); (c) cell volume of packed cells, the smaller the volume, the more rapid being the sedimentation rate; and (d) deviation of the sedimentation tube from the perpendicular position.

In connection with this last observation, the studies of F. Boerner and H. F. Flippin (J. Lab. and Clin. Med. 20:583 (Mar.) 1935) are of interest as presenting a simple method of assuring that blood sedimentation reactions are conducted with the sedimentation tube in a perpendicular position.

These workers used the Westergren sedimentation tube, suspended from a thumb-tack by means of a small hook made from a Gem paper-clip and a snugly-fitting cotter-pin inserted in the upper end of the tube.

After the tube has been filled with blood to the 200 mm. mark, the lower end is sealed by inserting it into a small rubber bulb which, by reason of a small window cut into the wall near the blind end, is easily slipped into position (when first moistened) without disturbing the column of blood. The arrangement is easily seen in the Fig. 1.

It is readily apparent that blood sedimentation is a complex phenomenon influenced by varied and complex factors which, in all probability, exert their effects upon surface tension, capillary attraction, or electrical charges of the cell or plasma.

Studies such as these have a definite clinical application, as suggesting that a phenomenon so readily influenced by so many factors holds but little promise of becoming of definite diagnostic or prognostic value.

As an indication of *activity*—without, however, furnishing any clue as to the nature of the activity,—the determina-

(2) that a comparison of the leukocyte count and sedimentation rate in 106 cases showed the latter to be the more accurate index; (3) that the comparison between the sedimentation rate and other clinical and laboratory findings (such as sputum, presence of moderately coarse râles, and symptomatic activity), while definite, was not as marked as that between the sedimentation rate and the roentgenogram; and (4) that the sedimentation rate quite accurately followed the course of the disease and in some cases gave warning of relapses before new shadows appeared in the x-ray plates.

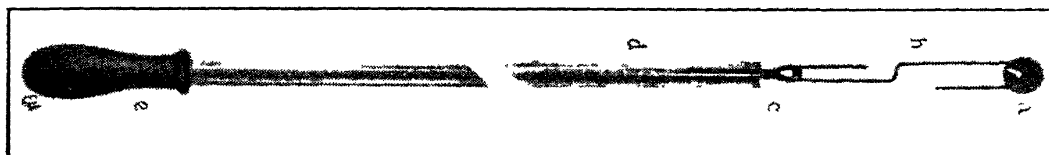


Fig. 1.—Drawing of the Westergren tube suspended from a thumb tack: (a) Thumb tack, (b) bent gem paper clip serving as a hook, (c) cotter pin, (d) Westergren tube, (e) rubber bulb with window. Boerner and Flippin: J. Lab. and Clin. Med.)

tion of the blood sedimentation rate possesses some clinical value. Its limitations, however, are only now arriving at a just appreciation.

The outstanding clinical applications of blood sedimentation reactions are still exemplified by their use in gynecology, as an index of the subsidence of *acute tubal inflammatory conditions*, and in tuberculosis, as an evidence of persisting or reawakening activity in pulmonary lesions.

In this latter connection, the recent study of W. O. Kelley (Am. Rev. Tuberc. 34:489, 1936) is of interest and practical value.

From a study of 1381 determinations on 290 cases of *pulmonary tuberculosis*, Kelley draws the following conclusions: (1) That there was a close correlation between the roentgenogram and the sedimentation rate as evidence of the activity of the tuberculous process;

The sedimentation rate in 80.5 per cent. of cases with *pleurisy* was abnormal.

Incidentally, Kelley suggests that a single reading at the end of one hour is quite practical for clinical purposes.

#### ANEMIA OF PREGNANCY.—

Within comparatively recent years, the studies of various investigators has focussed attention upon the anemia of pregnancy, not the pernicious, hyperchromic form, the clinical manifestations of which are striking and more or less compel attention, but more particularly the secondary, hypochromic type, the onset of which is more or less insidious and, too often, has escaped attention.

It is well recognized now that this secondary anemia of pregnancy is rather common, that it progresses *pari passu* with the progression of the pregnancy, and that it is related in some degree to food deficiency factors in its etiology,

as well as to certain deficiencies in gastric digestion associated with achlorhydria or hypochlorhydria.

Its obvious importance in the management of pregnancy has given rise, indeed, to the dictum that, next to the urine and blood-pressure, a blood count is of the greatest importance during pregnancy.

The subject has recently been reviewed by J. C. Corrigan and M. B. Strauss (J. A. M. A. 106:1088 (Mar. 28) 1936).

These investigators suggested in 1930 that the underlying cause of *hypochromic anemia* in pregnancy was a virtual deficiency of iron consequent upon gastric secretory defects in the presence of fetal blood requirements. This hypothesis was later verified by other investigators and is again corroborated by Corrigan and Strauss in an investigation of 200 women studied in the last 4 months of pregnancy.

The outstanding feature of the investigation is the demonstration that hypochromic anemia in pregnancy may be largely prevented by the routine administration of **iron** (0.5 Gm. or  $7\frac{1}{2}$  grains of ferrous sulphate daily), especially in the latter months of pregnancy.

**LEAD POISONING.—Blood in.**—R. A. McKinney and S. Rosenzweig (J. A. M. A. 106:1660 (May 9) 1936) have recently described a modified and, they believe, an improved method for the demonstration of stippled erythrocytes in lead poisoning.

The 3 reagents required are kept for convenience in covered Coplin jars. The technic is as follows:

Fix dried smear in acetone-free methyl alcohol for from 3 to 5 minutes and transfer directly to Wright's stain (staining time predetermined for each lot of stain used); wash in tap water and transfer to dilute ammonia water (2.5 c.c. of stronger ammonia water in 1000 c.c. of distilled water); dip up and down

rapidly until blue color runs from slide; wash in tap water, dry and examine.

The finely stippled or coarsely dispersed "basophilic aggregations" in the red blood cells appear distinctly black against the gray or pink of the stained cell. The white blood cells retain the usual nuclear stain.

The ratio of lead-affected cells to the normal red cells is determined by an adaptation of the Fonio platelet counting technic. A minute opening in a paper disk dropped into the ocular diaphragm gives a suitable counting field. The stipple cells and the normal red cells in each field are counted, but tabulated in separate columns, until 250 normal red cells have been counted. The number of stipple cells is then multiplied by 4, giving the ratio of such cells to 1000 normal cells. The number of thousands of red blood cells per cubic millimeter multiplied by the number of stipple cells per thousand cells, gives the approximate number of lead stipple cells per cubic millimeter of blood.

This staining method offers nothing fundamentally new; its chief advantage lies in the fact that a simplification and combination of two previous technics makes possible:

1. A rapid detection and enumeration of stipple cells in a spread which is also adequately stained for a differential count of the white blood cells.
2. The utilization of reagents usually found in any physician's office or clinical laboratory.
3. A technic which stains dried smears 2 months old as satisfactory as fresh dried smears.

While it has been commonly thought that the study of the leukocytes in lead poisoning was of little significance, attention was called in 1934 by A. E. Ferguson and T. Ferguson (J Hyg. 34:295 (Oct.) 1934) to the clinical value of the determination of the ratio of large mononuclear cells to small lymphocytes. These workers, from their studies upon shipbreakers subjected to a great hazard (caused by oxy-acetylene flames impinging on lead paint), concluded that an increase in the ratio re-

ferred to had even a closer relation to the clinical condition than the stippled cell count.

The ratio increased shortly after beginning work in this employment and as long as it remained above 2:1, there was little danger of the subjects showing lead poisoning. When it fell below 1:1, on the other hand, lead poisoning, if not already present, was imminent. In their opinion the periodical determination of this ratio in persons exposed to a lead hazard was more useful in preventing the incidence of lead poisoning than the determination of stippled cell counts.

These findings have been recently confirmed, and the conclusions advanced have again been emphasized by D. O. Shields (M. J. Australia 1:847 (June 20) 1936) after a study of this ratio in workers of the Mount Isa Mines, Limited, in Australia.

The procedure has the advantage of being independent of personal factors and variations of technic. Its only difficulty lies in the distinction between monocytes and large lymphocytes; both are therefore included in the classification of large mononuclear lymphoid cells.

Ferguson and Ferguson (*loc. cit.*) define such cells as being at least as large as a polymorphonuclear lymphocyte. Shields resorts to actual measurement by means of an ocular micrometer, and calls all cells 10 microns or more "large," and all cells of less than this diameter "small."

It is essential to the accuracy of this determination to have thin films (1 cell thick) to avoid distortion in the shape and apparent size of the cells. At least 50 lymphocytes should be counted in each film.

Shields concludes from his studies upon both normal individuals and those exposed to a lead hazard, that the ab-

sorption of lead causes a definite increase in the ratio of large lymphocytes (*plus* monocytes) to small lymphocytes; that a fall in the ratio below 2:1 in an individual exposed to a lead hazard is associated with definite symptoms, usually sufficiently severe to cause incapacity; and that the magnitude of this ratio is more closely associated with the clinical condition than is the stippled red cell count. As a rule, the more severe the case, the lower the ratio.

It would thus appear that the determination of this ratio is a simple and very useful index of the imminence or presence of lead poisoning and serves, also, as an accurate measure of its degree.

#### *Determination of Lead In Urine.*—

As the examination of the urine for lead is of great importance in the diagnosis and study of this condition, the new method described by J. R. Ross and C. C. Lucas (J. Biol. Chem. 111:285 (Oct.) 1935) is of interest and described below:

*Reagents.*—Redistilled water—prepared in a Pyrex all-glass still—should be used for all operations except preliminary rinsings.

1. Glacial acetic acid.
2. Citric acid solution, 10 per cent.
3. Perchloric acid, 72 per cent.
4. Hydrochloric acid, 1 N and 6 N.
5. Ammonium hydroxide, concentrated, 1 N and 0.075 N (or 0.5 per cent.).
6. Ammonium oxalate solution, saturated; or powdered ammonium oxalate.
7. Calcium chloride solution, 10 per cent. strength.
8. Hydrogen peroxide (30 per cent.).
9. Purified carbon tetrachloride. (Chloroform may be used as solvent. It has the advantage that the reagent dissolves in it much more rapidly than in carbon tetrachloride, but the latter is less volatile than the chloroform and, for colorimetry, is to be preferred.)

10. Purified dithizone solution in carbon tetrachloride, about 3 mg. per 100 c.c. Dissolve about 4 mg. of commercial dithizone in 25 c.c. of carbon tetrachloride. Extract with three 25 c.c. portions of 0.075 N (0.5 per cent.) ammonium hydroxide. This dissolves

the dithizone but not the impurities. Reject the carbon tetrachloride layer. Neutralize the aqueous layer to litmus with 1 N hydrochloric acid and extract the purified dithizone with several 15 c.c. portions of carbon tetrachloride. Dilute to 100 c.c. The solution should be kept in a Pyrex flask in the refrigerator and made up freshly every 3 days.

11. Sodium cyanide solution, 20 per cent.

12. Lead standards. 0.160 Gm. of crystalline lead nitrate made up to 1 liter with double distilled water. Two drops of lead-free nitric acid are added to a 100 c.c. aliquot, which is stored in a Pyrex vessel. This is Standard 1. One c.c. contains 0.10 mg. of Pb. One c.c. of Standard 2 contains 0.01 mg. of Pb. This is made by diluting 10 c.c. of Standard 1 to 100 c.c.

The solutions to be used are made from the best analytical grade of chemicals available. Regardless of the claims made on the label, all reagents should be tested for their lead content by the following procedure: A solution of the reagent under examination is made up as required for the test and a quantity equal to 3 to 5 times the amount used in the analysis is made just alkaline to bromothymol blue with ammonia. After the addition of a few drops of 20 per cent. sodium cyanide, the mixture is shaken in a separatory funnel with 1 c.c. of the purified dithizone solution. A cherry-red color indicates the presence of lead. Reagents containing more than 0.001 to 0.002 mg. of Pb in the quantities used in the method must be discarded and others tried. In this way the lead content of reagents from different chemical houses may be readily determined; those reagents containing the smallest amounts of lead should be used.

*Procedure.*—Adjust 100 c.c. of urine in a special glass-stoppered tube (or in a glass-stoppered graduated cylinder) to approximately pH 4.5 with bromocresol green indicator by the dropwise addition of glacial acetic acid. Add approximately 0.5 Gm. of powdered ammonium oxalate (or 10 c.c. of saturated ammonium oxalate solution) and mix. Then add 2 c.c. of 10 per cent. calcium chloride solution and again mix. The lead is in this way completely precipitated by entrainment with the calcium oxalate precipitate. After the mixture has stood for 20 minutes (or overnight) with occasional shaking, the open end of the tube is covered with a cigarette-paper, held in place by a rubber band, and centrifuged. The supernatant liquid is then discarded and the precipitate washed with about 15 to 20 c.c.

of double distilled water containing a few drops of saturated ammonium oxalate solution. The clump of precipitated calcium oxalate and uric acid is broken up with a glass stirring rod to insure thorough washing. It is then recentrifugated. After the wash water is decanted, the tube is inverted and allowed to drain on filter paper. This removes most of the phosphates which otherwise would interfere later in the procedure. Two c.c. of perchloric acid and 2 drops of 30 per cent hydrogen peroxide are added and mixed with the precipitate by agitation. The mixture is digested for at least 20 minutes on a micro-Kjeldahl digestion apparatus with a glass fume tube. While it is still hot, add 3 drops of the strong hydrogen peroxide (delivered cautiously down the side of the tube), and continue digestion for 3 minutes. When the mixture is cool, 5 c.c. or more of double distilled water are added to dissolve the perchlorates, followed by 3 c.c. of 10 per cent. citric acid solution, to prevent the precipitation of traces of phosphates which may still be present. Two drops of bromothymol blue are added and the solution is made *just* alkaline by the addition of 1.5 c.c. of concentrated ammonium hydroxide followed by the dropwise addition of this reagent. If it has been made too alkaline (causing a precipitate to form), adjustment is made with citric acid solution. The digested solutions should not be made alkaline, however, until just previous to extraction, as a precipitate tends to form on standing. If this has occurred, they are acidified to dissolve the precipitate and carefully made just alkaline.

If much lead is expected to be present, it is advisable to transfer the solution to a 15 c.c. volumetric flask and use only aliquot portions for subsequent procedures. The clear solution (or a 5 c.c. aliquot) is transferred to a 50 c.c. separatory funnel and 4 drops of 20 per cent. sodium cyanide solution are added. At this point the solution should be water-clear and the volume about 20 c.c. The mixture is then shaken vigorously with about 1 c.c. of purified dithizone solution. For extracting very small amounts of lead such as are found in normal urines (less than 0.015 mg.), a more dilute dithizone solution is preferable (one-half strength). The cherry-red solution of lead dithizone in carbon tetrachloride is drawn off and the extraction is repeated with 1 c.c. or diminishing portions of the dithizone solution until no further red color appears in the carbon tetrachloride. The lead in this way is

completely removed from the aqueous solution. After a little experience with the method, this extraction can be made to serve as a rough titrimetric estimation of the quantity of lead present. The supernatant solution, which assumes a yellow color owing to the excess dithizone being dissolved in the alkali, is discarded.

The red dithizone solution, after being washed with about 10 c.c. of 0.5 per cent. ammonium hydroxide containing 2 or 3 drops of the sodium cyanide solution (to remove any excess reagent), is made up to a definite volume with carbon tetrachloride and read in the Duboscq colorimeter against a known standard prepared in a similar way. This standard should be extracted at the same time from a suitable quantity of the lead standard. Since green colors are more easily read by some observers than red, it is sometimes advisable to change the color of the recovered lead solutions to the green by shaking with dilute (1:3) hydrochloric acid. The depth of the green color will be proportional to the amount of lead, provided the recovered samples have been washed free of excess reagent.

A distilled water blank should always be run at the same time as the test sample, in order to determine the amount of lead contamination from chemicals, glassware, etc. The amount of lead found in this water blank is finally subtracted from the amount determined for the test samples.

The dithizone solutions should be kept in glass-stoppered tubes away from bright light and read within an hour. Fading of the color is minimized by placing the tubes in the refrigerator until they are read. For determinations of less than 0.015 mg., total volume of carbon tetrachloride extracts should be kept within 5 c.c. This necessitates reading with the microcolorimeter attachment, or against a series of standards in a comparator block.

With this method Ross and Lucas regard the "normal" limits as 0.03 to 0.08 (average 0.05) mg. of lead per liter of urine (from determinations on 10 normal adults) for adults and 0.04 to 0.08 (average 0.06 mg.) in children (from determinations in 10 normal children).

These investigators cite the findings of Badham and Taylor (1925) of 0.02 mg. of lead per liter of urine for normal individuals in Sydney, Australia, and those of Litzner and Weyranch (1933), who reported 0.01 to 0.55 mg. of lead per liter of urine for normal adults in Germany.

### ALLERGY.—*Leukopenic Index.*

—The leukopenic index in allergy was developed from an observation by W. T. Vaughan (J. Allergy 5:601 (Sept.) 1934) in 1933 that, although the Widal colloidaloclastic reaction was not a reliable test for liver function, certain individuals allergic to milk reacted with leukopenia after the ingestion of milk.

Further studies by the same worker (*Ibid.* 6:78 (Nov.) 1934; 6:421 (July) 1935) established the clinical value of this procedure in the study and recognition of allergy. This conclusion has been corroborated by various other investigators, among whom may be noted H. J. Rinkel (*Ibid.* 7:356 (May) 1936; J. Lab. and Clin. Med. 21:814 (May) 1936), M. Zeller (Illinois M. J. 69:54 (Jan.) 1936; J. Lab. and Clin. Med. 21:1274, 1936), and L. P. Gay (J. A. M. A. 106:969 (Mar. 21) 1936).

The clinical value of this procedure seems thus well and definitely established. While not 100 per cent. accurate or reliable, it is still about 20 per cent. more reliable than the skin test to foods (scratch, intracutaneous, or both).

The determination of the leukopenic index is a very simple procedure and consists of the following:

Two fasting white counts are made upon the patient in the morning at 10-minute intervals, after which the patient eats the food for which he is to be tested. Following this, 3 additional counts are made at half-hour intervals. If any one of the postprandial counts falls more than 1000 below the mean of the two fasting counts, the index is considered positive. A drop of less than 1000 is considered a negative index unless maintained throughout the three counts, in which case it is described as "general low range, probably positive."

Certain precautions are necessary in the interest of accuracy: (1) The same pipette and counting chamber must be used throughout each study; (2) the pipettes must be shaken for 3 minutes to ensure even distribution; (3) counting chambers must be filled evenly and to approximately the same degree each

time; (4) at least 200 cells (eight 1 mm. squares) are counted in each determination; and (5) the blood must be obtained from a freely flowing needle puncture.

As is properly emphasized by Vaughan, the leukopenic index is to be regarded as an adjuvant to rather than a substitute for other methods of allergic study. As such, its value seems to have been demonstrated.

The reliability of the leukopenic index as an index of allergy to foods has been questioned by some workers because of the well known variability of the leukocyte count, both fasting and postprandial.

As W. T. Vaughan (J. Lab. and Clin. Med. 21:1278, 1936) points out, however, these variations occur in the afternoon rather than the morning, and the leukopenic index determinations are made in the morning.

Moreover, the studies of E. Ponder, G. Saslow, and M. Schweizer (Quart. J. Exper. Physiol. 21:21 (Apr.) 1931), who counted 800 cells for each determination, have shown that the variations are not generally as great as reported by others. This they believe is due to the possibility of technical errors, especially faulty distribution.

It will be noted, in the description of the determination of the leukopenic index, that this point is emphasized.

Vaughan has carefully studied the question, and in a total of 1000 fasting counts on 500 persons (each having 2 counts at 10-minute intervals), found only 1 per cent. showing a fasting fluctuation of over 2000 cells.

As he says, while the leukopenic index is not 100 per cent. accurate or reliable, it is nevertheless about 20 per cent. more reliable than skin tests, and so gives to the allergist a simple and valuable addition to his diagnostic armamentarium.

**ALLERGIC RHINITIS.**—The so-called common colds, particularly when recurrent, may at times have an allergic basis, the determination of which is often, even when suspected, a matter of some difficulty. While a pale, boggy, nasal membrane is accepted, when present, as significant, it is not always present and so cannot serve as a reliable and consistent indication of allergic rhinitis.

D. M. Cowie and B. Jimenez (Arch. Int. Med. 57:85 (Jan.) 1936) call attention to the value of cytological examination of nasal smears in the study of such conditions.

In sensitized persons with nasal discharge, their studies showed a distinct increase in the number of eosinophiles when a differential count was made on the nasal smear, and their investigations lead them to conclude that an eosinophile count of 20 to 25 per cent. indicates that the patient is allergic.

While eosinophilia occurs in the nasal smears of persons both with and without allergy to pollen, it is more marked in those who present an associated epidermal sensitization.

During an infectious cold in such individuals, there is a reversal of the cytologic picture of the nasal smear and the eosinophile count may be reduced far below that ordinarily seen in the allergic individual.

No definite relationship between the differential counts of nasal smears and the blood, made simultaneously, could be demonstrated.

Cowie and Jimenez conclude that the presence of eosinophilia in the nasal smear, particularly when "colds" are recurrent, may be of value in suggesting a possible allergic basis and that the consistent appearance of such "eosinophilous" colds may serve as an indication for sensitization studies in such an individual.



**AGGLUTINATION REACTIONS.**—It is now rather generally accepted that, as originally stated by Felix, the presence of "O" agglutinins is indicative of infection, while the "H" agglutinins show little or no relation to the actual course of the disease and arise, in the majority of instances, from vaccination.

While both "O" and "H" agglutinins can be detected when a living culture is used in the performance of the agglutination test in the study of enteric fevers, this is not the case when—as is the common custom—a single formalized or phenolized antigen is used. With killed antigens, "O" agglutination is inhibited, possibly, it has been suggested, because the "O" agglutinins, which are of flagellar origin, are kept apart mechanically by the hardened flagella of the killed antigen.

These facts have had an influence upon the technic of agglutination tests, because if living antigens are used with which, as has been stated, both types of agglutinins may be detected; they must not only be transplanted and tested daily for standardization, but they must also be tested for smoothness at regular intervals (3 weeks).

To obviate these technical difficulties, H. Welch and C. A. Stuart (J. Lab. and Clin. Med. 21:411 (Jan.) 1936) have proposed a rapid slide test based more or less upon that devised by Huddleson in the study of undulant fever.

The method was further modified by H. Welch and F. L. Mickle (Am. J. Pub. Health 26:248 (Mar.) 1936), and, from an extensive comparison with the macroscopic test-tube method, seems delicate, reliable, and a useful addition to the laboratory methods available for the study of enteric diseases.

The technic, therefore, is described in detail as follows:

**PREPARATION OF ANTIGEN.**—While the description to follow applies specifically to the preparation of typhoid antigens, the same method is used for the preparations of *Salmonella paratyphi* and *S. schottmuelleri*.

**Preparation of Typhoid "H" Antigen Suspension.**—1. A strain of *E. typhosa* of known antigenic make-up, which has been carefully checked for smoothness, is grown on agar (pH 7.0 to 7.2) in Blake bottles for 24 hours at 37° C.

2. Cover the surface of the medium with 12 per cent. solution of sodium chloride containing 0.5 per cent. formalin (not more than 5 c.c. to a bottle) and allow to stand 1 to 2 hours. Then wash the growth from the surface of the medium by gently rocking the bottle.

3. Pool the concentrated suspensions and filter through at least 8 layers of cheese-cloth to remove clumps.

4. Centrifuge for 1 to 2 hours at high speed, to pack the organisms as completely as possible.

5. Remove and retain the supernatant fluid and record the volume of packed organisms.

6. For each cubic centimeter of packed organisms add 5 to 7 c.c. (not more!) of the supernatant fluid.

7. Again filter this concentrated suspension through 8 layers of cheese cloth, when it is ready for titration.

This suspension contains "O" as well as "H" antigen.

**Preparation of "O" Antigen Suspension.**—The same strain used for the preparation of the "H" (flagellate) antigen is used for the preparation of "O" (somatic) antigen suspension.

1. Grow the organisms on agar (pH 7.0 to 7.2) in Blake bottles for 48 hours at 37° C.

2. Wash off the growth as before with 12 per cent. sodium chloride solution containing 0.5 per cent. formalin and pool the suspensions.

3. To the pooled suspensions add 3 volumes of 95 per cent. alcohol and shake the flask vigorously for 10 minutes.

4. Incubate 24 hours at 37° C., at the end of which period the antigen appears as a white flocculent mass on the bottom of the flask.

5. Siphon off and discard the greater portion of the alcohol.

6. Centrifuge the suspension for 1 to 2 hours until the organisms are as tightly packed as possible.

7. Remove the supernatant fluid and to each 1 c.c. of packed organisms add 5 to 7 c.c. of

12 per cent. salt solution. The suspension is then ready for titration.

**ANTIGEN TITRATION.**—The antigen dilution desired is one which will show in the slide test an agglutination in agreement with that obtained with a similar dilution in the macroscopic tube test, which titer is previously ascertained.

The usual range of dilution in macroscopic tests is from 1:20 to 1:640.

The standard tube test used by Welch and Mickle (*loc. cit.*) utilizes as antigens live

**TITRATION OF SLIDE TEST ANTIGENS.**—1. In each of 4 test tubes place 0.5 c.c. of antigen to be titrated and then add 0.1, 0.2, 0.4, and 0.5 c.c. of the retained supernatant fluid.

In titrating the "O" antigen, 12 per cent salt solution is added, since this supernatant fluid contains flagellated organisms.

2. The diluted antigen from each tube is then tested on the slide with serums of known test tube titer, as follows:

(a) On slides prepared as described below, place 0.03 c.c. (1 drop) of diluted antigen and

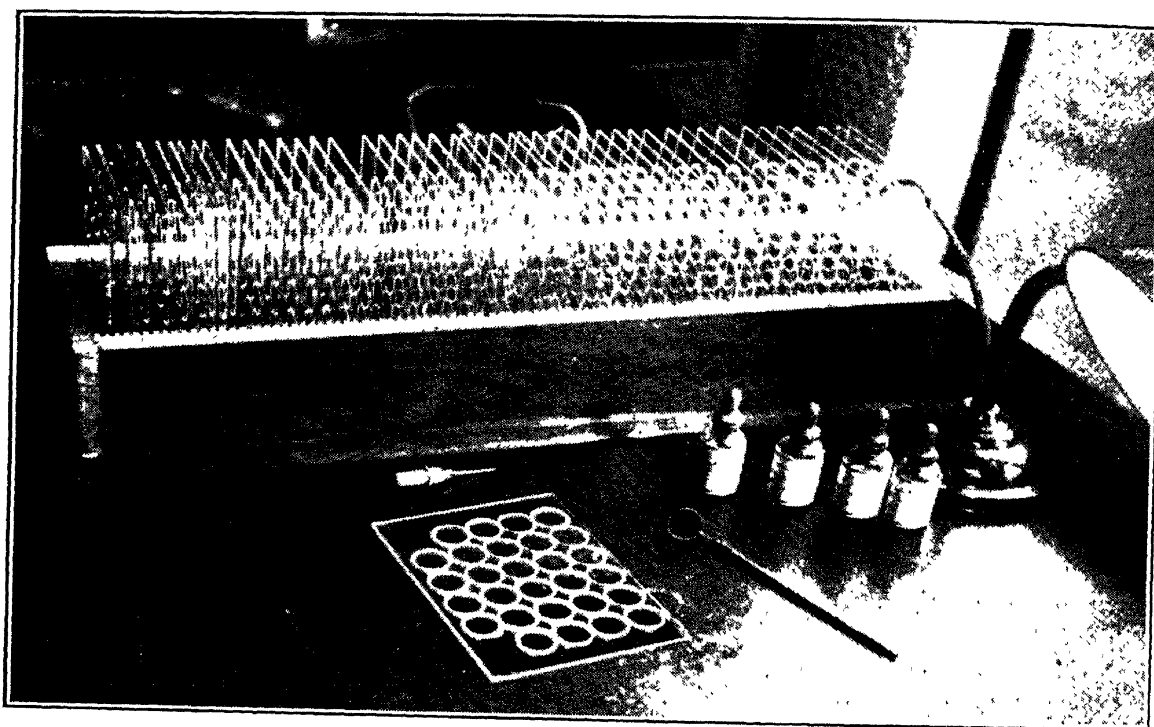


Fig. 2.—Showing slides with wax rings, four types of antigen used, wire loop, and Huddleson dropper. (Welch and Stuart: J. Lab. and Clin. Med.)

suspensions of *E. typhosa* "H," *S. paratyphi*, and *S. schottmuelleri*, and an alcohol treated suspension of *E. typhosa* for "O" antigen, all suspensions being diluted to a turbidity of 6.9 on the Gates apparatus (F. L. Gates: Jour. Exper. Med. 31:105, 1920).

A series of serum dilutions (negative, partially positive and strongly positive serums are used for all titrations) from 1:10 to 1:320 is set up in test tubes in 0.5 c.c. amounts.

To each tube 0.5 c.c. of antigen is then added, making a final dilution range of from 1:20 to 1:640.

The tube tests are incubated at 52° C. for 3 hours and refrigerated overnight, when the final readings are made.

add the following amounts of each known serum: 0.08, 0.04, 0.02, 0.01, 0.005, and 0.002 c.c. The dilutions obtained correspond to those in the macroscopic test (1:20 to 1:640).

(b) Starting with the highest dilution (0.002 c.c. of serum), mix the antigen and serum with a toothpick.

(c) Rock the glass slide back and forth 15 to 20 times.

(d) Read the agglutination at once by holding the slide over a desk lamp so that the light is transmitted through the slide but not directly into the eyes of the observer.

Readings are recorded as: Plus 4 (complete agglutination); plus 3 (75 per cent.); plus 2 (50 per cent.); plus 1 (25 per cent.); plus-

minus (faint to 25 per cent.); and zero (no clumping).

The antigen dilution showing no clumping with negative serums, complete clumping with a clear background with all dilutions of strongly positive serums, and which gives with partially positive serums the titer shown in the macroscopic test is the proper dilution for the slide test. The titers obtained in both tests should agree to a plus-minus result.

*Apparatus Required for Slide Test.*—For the measurement of the antigen suspension the dropper described by I. F. Huddleson and E. Abell (J. Infect. Dis. 42: 242 (Mar.) 1928)

The rings are made with a wire loop, made by tightly winding No. 28 gauge wire around a 1-inch test tube; the loop thus formed is then wound (single thread) with No. 12 thread and forced into a regular platinum loop holder. The same apparatus is used in the preparation of slides for the microscopic Kline test in syphilis.

A number of slides can be prepared at one time or, where only a few tests are to be done, only a few slides are prepared in advance.

Slides may be washed off in hot, running water, cleaned on both sides with Bon Ami,

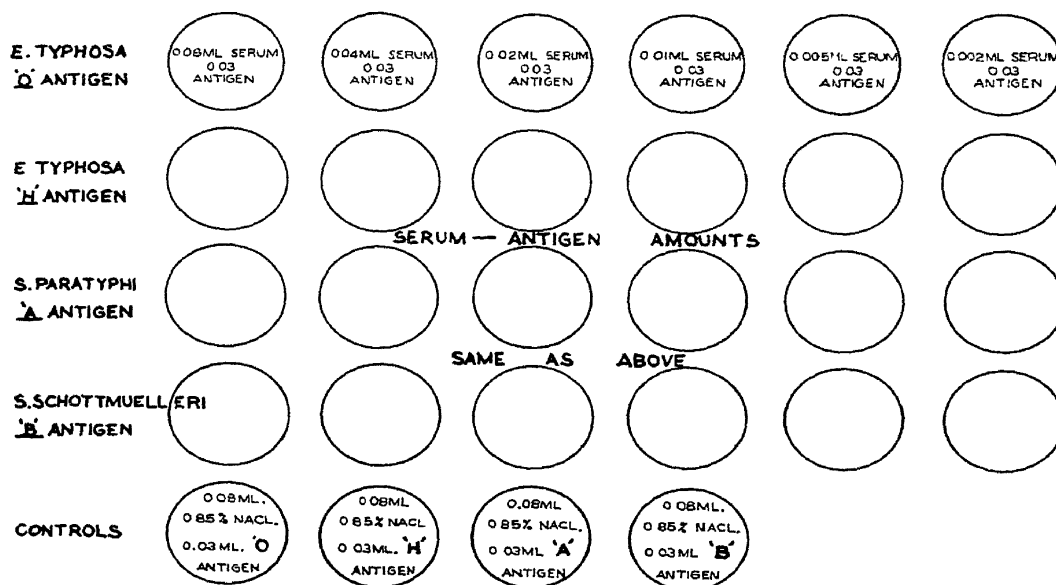


Fig. 3.—Showing serum-antigen amounts used in slide test.  
(Welch and Mickle: Am. J. Pub. Health.)

is most convenient, although a Kahn pipette may be used.

Such a pipette may be prepared by drawing out thickwalled glass tubing of  $\frac{1}{8}$ -inch bore and cutting the capillary end at 0.07 diameters (B. & S. gauge), and will deliver approximately 0.03 c.c. per drop.

Glass slides for the conduct of the test are made from ordinary picture-frame glass 7 inches long, 5 inches wide, and  $\frac{1}{16}$  inch thick. Where but few tests are done, such slides may be prepared from old photographic plates from which the emulsion has been cleaned.

Twenty-eight 1-inch wax rings are placed on each slide in 4 rows of 6 rings and 1 row of 4, using a mixture of 70 per cent. paraffin (M. P. 48° C.) and 30 per cent. petrolatum heated to 130° to 140° C.

dried, and wiped off with a clean cloth, when they are again ready for imprinting the wax rings.

The apparatus required is shown in the Fig. 2.

*Technic of Slide Test.*—In the routine diagnostic slide test, the patient's serum is pipetted onto a 5-inch by 7-inch glass slide in the following amounts: 0.08, 0.04, 0.02, 0.01, 0.005, and 0.002 ml. using a Kahn pipette (0.2 ml. graduated in thousandths). In the fifth row (used only for the first test each day), 0.08 ml. of 0.85 per cent. salt solution is added to each of the four rings for controls on each of the four antigens. A drop of "O" antigen is added to each of the serum amounts in the first row and to the first ring in the fifth row. Similarly, a drop of "H" antigen is added to

each of the serum amounts in the second row and to the second ring in the fifth row. *S. paratyphi* is added to the third row and *S. schottmuelleri* to the fourth row, each with the appropriate controls in the third and fourth rings respectively in the fifth row. The above serum-antigen mixtures in each row correspond to dilutions of 1:20 through 1:640 in the tube test. All antigens are shaken gently but well before using. Each row of serum-antigen mixture is thoroughly mixed with a separate toothpick or applicator, starting with the smallest amount (0.002 ml.) of serum and working from right to left. After mixing, the glass slide is gently rocked back and forth 15 to 20 times and the degree of clumping estimated. The type of agglutination obtained with the "O" antigen does not correspond to the typical small flaking or granular agglutination obtained in the tube test, and hence "O" and "H" agglutination cannot be differentiated by appearance. This is no disadvantage, since both types of antigens are used.

The set-up is apparent from Fig. 3.

**TRANSFUSION.—Relation of Minor Blood Agglutinins to Posttransfusion Reactions.**—It is now well recognized that the final criterion in the selection of a donor is not blood grouping, but the results of a direct compatibility reaction. Nevertheless, even when this has been done, both physician and laboratory worker may infrequently be embarrassed by posttransfusion reactions which at first glance are puzzling and inexplicable.

The existence of minor agglutinins (the subgroup agglutinins; Landsteiner's irregular isoagglutinins and normal cold agglutinins; the pathologic cold agglutinin; and the rouleau-forming property) has been the subject of numerous and interesting studies by various workers. Very little attention has been paid to them, however, as possible sources of posttransfusion reactions, although their importance in this connection has been commented upon by some few observers.

Prompted by the occurrence of a severe posttransfusion reaction conse-

quent upon failure of the usual tests to detect a strong autohemagglutinin in the patient's serum, W. P. Belk (Am. J. M. Sc. 191:827 (June) 1936) has studied the question anew with the particular purpose of devising a method for the detection of incompatibilities due to both major and minor agglutinins, including the autoagglutinin, which latter is often missed by the ordinary technic in which clots are allowed to become chilled and serum-cell mixtures incubated at room temperature. Where the serum-cell incubation is conducted at 37° C., as is the case with many workers, the effect of autoagglutinins is inhibited, as is seen from what follows.

Autoagglutinin is characterized, first, by the fact that its property of clumping erythrocytes is entirely lost at 37° C., but becomes increasingly evident as the temperature lowers, reaching a maximum at 0° C., at which temperature the agglutinin is fixed to the cells, clumping them in masses. The reaction is reversible, the agglutinin becoming detached and the cells "unclumped" as the temperature rises. This phenomenon is a property not of the cells, but of the serum. Though not specific, being capable of acting on the erythrocytes of many, if not all, animals (panagglutinin), it is still a true agglutinin, being absorbable and not influenced by lecithin. Whether it is related to rouleaux formation is a matter of discussion.

The method devised by Belk for its detection follows:

Venous blood collected in sterile test tubes is allowed to clot at 37° C., or if previously chilled, is warmed to 37° C. After removal from the incubator, serum is promptly centrifuged and pipetted off to prevent any but slight chilling. The cells are collected in 1.5 per cent. sodium citrate in normal saline (or other suitable fluid) and washed twice in saline warmed initially to 37° C. These steps assure a maximum of autoagglutinin in the serum and its removal from the cells. On clean glass

microslides ringed with a wax pencil the following mixtures are prepared: patient's serum and patient's cells, patient's serum and donor's cells, donor's serum and donor's cells, donor's serum and patient's cells. The suspensions are light, about 1 per cent., as an excess of cells masks agglutination. The slides are placed in the refrigerator (5° C. to 10° C.) for 30 minutes, then removed, one at a time, gently agitated, and observed at once under the microscope. Agglutination is recorded as from 0 to +4. A second observation is made after about 10 minutes at room temperature (or 37° C.) to note reversal of agglutination. The following is an example of the application of the technic from the protocols:

- Patient's serum plus patient's cells, +4.
- Patient's serum plus donors' cells, +4.
- Donor's serum plus patient's cells, 0.
- Donor's serum plus donor's cells, 0.

"Agglutination in patient's serum completely disappeared after 10 minutes at room temperature; no rouleaux. Diagnosis—strong auto-agglutinin in patient's serum. Advise no more than 100 c.c. blood be given at one time."

**"Canned Blood" for Transfusions.**  
—Over 10 years ago, Baldwin, reviewing the literature of transfusion, commented upon "the epidemic of transfusion which passed over the profession from 1863 to 1884" and expressed the belief that a similar period of enthusiasm was about to dawn. It is improbable that there will be any general denial of the truth of this prediction.

Perhaps the most startling if not the newest development in the field of blood transfusion, is the relatively recent announcement of the successful use of cadaver blood (popularly referred to as "canned blood") for transfusion.

The genesis of this procedure was the work of Shamov in 1928 on dogs, followed by the investigations of M. G. Skundina and S. I. Barenboim (Novy khir. arkhiv 101, 1932) in 1932 upon the oxygen exchange before bleeding, after partial exsanguination, and after transfusing these animals with blood taken from dogs killed a few hours before.

Their experiments demonstrated that animals dying of acute anemia could be revived by the transfusion of cadaver blood and that such blood not only raised the oxygen content of the blood immediately, but was able to participate actively in the gaseous exchange. They further demonstrated that when the cadavers were kept at a temperature of 1 or 2° above zero, the blood in the cadaver vessels preserved its living properties for from 6 to 7 hours.

In 1935 M. G. Skundina, A. W. Rusakov, and R. E. Ginsberg (Sovet. khir. 7:194, 1934; *Ibid.*, No. 6, p. 78, 1935), in a study of cadaver blood in some 500 cadavers, found that coagulation of the blood and further behavior of the coagulum depended, in the given case, upon the cause of death and duration of the antemortem agony.

Blood secured from individuals dying rapidly (accident, apoplexy, drowning, cardiac disease, etc), coagulated rapidly if removed within a few hours after death; such coagulated blood, however, within 1½ to 1½ hours returned to the fluid state and thereafter would not coagulate again. Agitation or warming of the blood accelerated the fibrinolysis, while saturation with oxygen retarded it.

This phenomenon of fibrinolysis in the blood of individuals dying suddenly is of practical significance in that such blood can be preserved in a fluid state without the addition of an anticoagulant.

The results of these studies, coupled with the difficulty of securing an adequate supply of donors for the numerous transfusions required by "the special conditions" existing in the Surgical Clinic of the Central Emergency Hospital in Moscow, led S. S. Yudin, Chief of Clinic, to attempt the use of cadaver blood in the transfusions of human beings and to report upon 924 such transfusions. (J. A. M. A. 106:997 (Mar. 21) 1936.)

The technic of securing such blood is simple: The jugular vein is severed and a glass cannula to which a rubber tube is attached is introduced into each end of the vein. The cadaver is then placed in the Trendelenburg position and the blood allowed to run into a 500 c.c. glass flask, which is then stoppered with cotton and placed in the refrigerator, where it may be kept for one month.

The question of terminal, agonal bacterial invasion of the blood stream at once comes to mind. Yudin reports, however, that Skundina and Rusakov, following the postmortem injection of methylene blue, were unable to demonstrate the dye in blood from the jugular vein; that blood flowing from this vessel drains the systemic veins flowing from the superior and inferior vena cavae and not those of the lesser and portal circulations; and cites observations of Shamov that blood in the mesenteric veins is the first to become infected after the death of an animal.

As, at room temperature, infection from the bowels enters these veins within 20 hours, Yudin fixes the limit of usability of cadaver blood at 6 hours for the summer and 8 in the winter.

The technic of transfusion consists of warming the blood to body temperature by placing the flask in warm water, after which the blood is passed through a gauze filter into the vessel from which it is to be transferred.

Transfusion may be done with a syringe or by the gravity method. It should be preceded by the introduction of physiologic saline solution and the first 10 to 30 c.c. of blood given *slowly* as a biologic test for incompatibility.

Providing the body has not been damaged, from 2 to 3.5 liters of blood can be obtained from a cadaver. To secure the maximum amount, the most suitable cadavers are said by Yudin to be those killed by electric current, those

dying of angina pectoris, and those who have committed suicide by hanging.

It is obvious, of course, that sterility and Wassermann tests must be made before preserved cadaver blood can be used for transfusion. No mention is made in this abstract, however, of blood typing or direct compatibility tests, the latter especially being in this REVIEWER'S opinion the *sine qua non* for the selection of a suitable donor.

Yudin has not observed any toxic manifestations in a series of 924 cadaver blood transfusions and claims for the procedure the advantages that an ample supply of blood can be kept on hand for all emergencies; that such blood can be shipped long distances from a central station; and that the therapeutic effect of such transfusions in no way differs from those with blood from living donors.

The particular advantage emphasized by Yudin is the saving of the time necessary to call a donor and determine his suitability when the emergency and the necessity for transfusion are acute.

Apart from the startling and somewhat gruesome nature of this proposal, it is not quite clear just how it may be efficiently safeguarded from the possibility of transmitting disease to the recipient. While it is naturally to be assumed that the cadavers selected would be those of apparently healthy individuals, and while, to pass muster, such blood must be free from serological evidence of syphilis, Yudin numbers among the suitable cadavers those of individuals dying of angina pectoris and apoplexy, whom it is difficult to accept as having been previously in good health.

However, as the procedure has been shown to be feasible, and as it has been applied in a rather large series, it deserves at least a summary and review.

**HEMATOLOGIC TECHNIC.—**

**Preservation of Blood Films.**—T. K. Rathmell and H. W. Jones (J. Lab. and Clin. Med. 20:954 (June) 1935) have described a cheap, rapid, and simple method for the preservation of blood films, the details of which follow.

The method consists of the application of a thin coating of lacquer to a clean, dry, prepared blood smear after staining. The lacquer is a commercial product. If, upon standing, it should become cloudy, the transparency may be readily restored by the addition of a small

**Serum Protein.**—A rapid method for the estimation of serum protein has been described by R. O. Bowman (J. Lab. and Clin. Med. 21:1092 (July) 1936).

**REAGENTS.**—1. Protein Stock Standard Solution: 20 c.c. of fresh clear human serum are diluted to 200 c.c. in a volumetric flask with 15 per cent. sodium chloride solution. Mix and filter. Add a few crystals of thymol and the solution will keep for 6 months or more in the ice chest. Total nitrogen of this filtrate is determined by the micro-Kjeldahl method and nonprotein nitrogen is determined on a sample of the original serum by the Folin-Wu method. The total nitrogen of the filtrate, minus one-tenth of the nonprotein nitrogen of

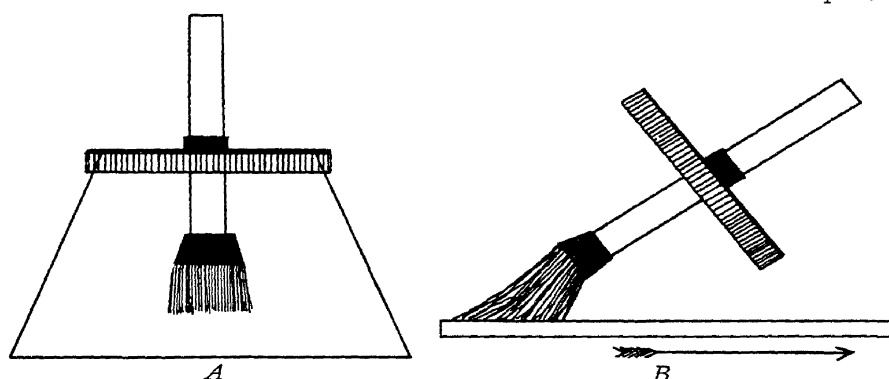


Fig. 4—A. Commercial glass jar with sable brush soldered in place. This is an air-tight receptacle for lacquer. B. Method of coating blood film. (Rathmell and Jones: J. Lab. and Clin. Med.)

amount of "transparentizer," obtainable from the lacquer supply source.

As a container, a commercial glass jar with an air-tight cover is recommended. The lacquer is applied with a No. 16 Sable brush, obtainable from any art supply company.

The slide must be dry and the lacquer applied in a thin, smooth layer with one stroke of the brush which should not carry an excess and is best wiped off on the rim of the glass jar before touching the slide.

The method is clear from the Fig. 4.

In slides so preserved there is little if any distortion of the cells. The lacquer dries rapidly, even in damp weather; is not affected by cedar oil or xylol; and has a refractive index approximating that of glass.

the serum, gives protein nitrogen, and protein nitrogen multiplied by 6.25 gives the protein content of the filtrate.

2. Protein Standard Solution: The stock standard is diluted with distilled water so as to contain 30 mg. per 100 c.c. of solution. This standard keeps for one year when preserved with thymol and kept in the ice chest.

3. 5 Per Cent. Sulphosalicylic Acid: Dissolve 50 Gm. of C. P. sulphosalicylic acid in distilled water and make up to a liter. Filter. This keeps indefinitely.

4. 22.2 Per Cent. Sodium Sulphate: 111 Gm. of anhydrous C. P.  $\text{Na}_2\text{SO}_4$  are dissolved in distilled water with the aid of heating to  $37^\circ \text{C}$ . in a 500 c.c. volumetric flask. The volume is made up to the mark at this temperature. With purified salt, filtering is not necessary. This reagent is kept at  $37^\circ \text{C}$ . in the incubator to prevent crystallization of the salt at room temperature.

5. 0.9 Per Cent. Sodium Chloride.

**METHOD.**—Exactly 0.2 c.c. of blood plasma or serum is diluted by adding 39.8 c.c. of

normal saline from a buret. If the determination is to be run at once, distilled water may be used instead of the saline.

After thorough mixing, 2 c.c. of the diluted serum is pipetted into a test tube and 2 c.c. of standard protein solution is pipetted into a similar tube. To each add 2 c.c. of 5 per cent. sulphosalicylic acid and mix thoroughly by rotating the tubes. Compare in the colorimeter.

*Calculation.*— $R \times 6 =$  Gm. protein per 100 c.c. where R is the ratio of depth of standard to depth of unknown solution.

For albumin determination, the globulins are precipitated according to the Howe method, 1 volume of serum to 30 volumes of 22.2 per cent. sodium sulphate, let stand for 4 hours or more in the incubator and filtered until clear. To 1 c.c. of the filtrate add 3 c.c. of distilled water and 4 c.c. of 5 per cent. sulphosalicylic acid. Mix and compare with a standard as above.

*Calculation.*— $R \times 3.72 =$  Gm. albumin per 100 c.c.

The method seems to be applicable to all serums and plasmas and is suitable for use in the average clinical laboratory.

The results are not influenced by moderate changes in the pH of the diluted sample, nor are they affected by the presence of oxalate. Because of the large dilution factor, any changes in pathologic bloods have little or no effect on the final result.

**SPINAL FLUID.—New Colloidal Gold Method.**—The innumerable methods published for the preparation of goldsol solution for the conduct of the Lange test evidence the difficulties attendant upon the preparation of satisfactory solutions. The method of D. P. Borowskaja (Ztschr. f. Immunitätsforsch. u. exper. Therap. 82:178 (May 8) 1934) has now, however, replaced them all as being simple, rapid and found entirely satisfactory after extensive trial.

**REAGENTS.**—1. One per cent. solution of gold chloride.

2. One per cent. solution of sodium citrate.

**METHOD.**—To 100 c.c. of cold or warm water in an Erlenmeyer flask add 1 c.c. of the 1 per cent. gold chloride solution and heat to boiling. Then add slowly 5 c.c. of the sodium citrate solution. The color change begins at once and is complete in from 1 to 3 minutes.

In this method the use of double distilled water as well as the numerous other special precautions described in other methods have been found to be entirely unnecessary. Goldsol prepared by this method is reliable, delicate, gives typical reactions, and is quite stable.

**Staining Technic for Blood in Spinal Fluid.**—J. Q. Griffiths, E. Roberts, and W. A. Jeffers (J. Lab. and Clin. Med. 21:1208, 1936) recently described a staining technic applicable to the differentiation of old and recent hemorrhage in the spinal fluid, which seems worthy of trial.

The method depends upon the assumption, the correctness or incorrectness of which has yet to be proved, that the erythrocyte is rich in lipid content as compared to the spinal fluid, and that in time some alteration of lipid distribution might occur.

The procedure is simple, as follows:

1. The smear of spinal fluid is permitted to dry spontaneously. Drying must be thorough (15 to 30 minutes).

2. While fixing does not seem to be essential, if desired, the smear may be passed through the flame several times, care being taken to *avoid overheating*.

3. Immerse the smear in 50 per cent. alcohol saturated solution of Sudan III for 20 minutes.

4. Rinse thoroughly in several changes of distilled water and blot dry with filter paper. *Never permit the smear to dry in air!*

5. Cover with glycerin, mount with a coverslip and examine. The preparations are not permanent and fade in a day or so.

In erythrocytes arising from fresh hemorrhage, they appear as round, homogeneously staining pale yellow discs. Where the hemorrhage is 24 hours old, the majority of the erythrocytes show central, unstained areas, giving the peripheral stained portions the appearance of rings.



As fresh blood mixed with saline presents the same appearance as fresh blood in the spinal fluid, this may be used as a standard of comparison.

### BACTERIOLOGY. — DIPHTHERIA.—*Rapid Culture Method.*

—The method described by M. B. Brahdy, M. Lenarsky, L. W. Smith, and C. A. Gaffney (J. A. M. A. 104:1881 (May 25) 1935) has now been found reliable and of practical application and value and therefore warrants description. That there is nothing new under the sun is exemplified by the fact that they recall that this method was first mentioned by Falger 36 years ago, but never published.

The procedure is quite simple: Sterile cotton swabs are impregnated with undiluted, unheated horse serum to which no preservative has been added. (Horse serum preserved with chloroform may be used, however.) The surplus serum is then removed by pressing the swab lightly against the wall of the test tube and the serum coagulated on the surface by heating the swab lightly over the flame. Swabs so prepared are used to take nose and throat cultures in the usual manner, replaced in their sterile tubes, incubated, and examined after 2 to 4 hours. In emergency, incubation may be carried out in the physician's vest pocket. Smear preparations are made directly from the swab and stained as usual.\*

This method makes it possible to determine the presence or absence of *B. diphtheriae* in 4 hours instead of the usual 18 hours necessitated by the incubation of a Loeffler slant, and, in addition its rapidity and simplicity, renders the method applicable in the absence of an incubator.

It has proved quite useful in the study of carriers as well as in the routine bacteriological diagnosis of diphtheria.

If it is desirable, as it often is, to determine whether or not the organisms

found are virulent, the following procedure is both rapid and effective:

A 4-hour swab culture found to be positive is transplanted to a Loeffler slant. After 18 hours incubation the diphtheria colonies are fished and the presence of *B. diphtheriae* thus corroborated. The surface growth is then emulsified and used for intracutaneous inoculation of guinea-pigs.

While pure cultures are preferable for virulence tests, Brahdy and his colleagues obtained satisfactory results with the procedure as described.

### SPIROCHETES, SPIRILLA, SPERMATOOZOA, and RELATED ORGANISMS.—*Rapid Method for Demonstration.*—A. J. Gelarie (J. Lab. and Clin. Med. 21:1065, 1936) describes a method easily and rapidly applied and giving clear-cut, and definite pictures.

REAGENTS.—1. Fixing Solution: Dissolve 2.5 Gm. of recrystallized zirconyl chloride ( $ZrOCl_2$ ) in 100 c.c. of 10 per cent. sodium chloride solution.

2. Citric Acid Solution: 10 per cent. solution of recrystallized citric acid in distilled water. To avoid fungus formation, add a few thymol crystals.

3. Staining Solution:  
Gentian violet ..... 0.25 Gm.  
N/10 sodium lactate solution 100 c.c.

The pH of this solution should be (or, if necessary, should be adjusted to be) approximately 8.4.

4. Mercuric Iodide Solution: 0.5 Gm. of mercuric iodide dissolved in 100 c.c. of 0.5 per cent. potassium iodide solution.

5. Counterstain:  
Methylene blue ... 0.2 Gm.  
Distilled water ... 100 c.c.  
Dissolve and add... 0.2 Gm. of phenol.

METHOD.—1. Prepare a thin smear and allow to dry in air. *Do not dry over the flame!*

2. Cover with fixing solution for 5 seconds and wash with water.

3. Cover with a few drops of citric acid solution, allow to remain 10 seconds, and wash off with water.

4. Cover with staining solution for 30 seconds and wash off with water. (For photographic purposes stain with aqueous carbol fuchsin instead of methylene blue.)

\* Prepared swabs are now commercially available.

5. Cover with a few drops of the mercuric iodide solution and at once wash with water. (This solution may be replaced by 0.01 per cent. solution of picric acid which, however, causes some precipitation).

6. Wash, dry with filter paper, and examine under the oil immersion.

In the study of spermatozoa, the counter-stain should be omitted, to avoid overstaining.

Spirilla are stained a deep purple under artificial light; deep blue with natural light (daylight); *Sp. pallida* is also purple under artificial light.

**PERTUSSIS.—New Diagnostic Methods.**—The recognition of atypical whooping cough in the absence of the pathognomonic whoop is a matter of great difficulty, important as it may be in the dissemination of this disease. The difficulty arises from the fact that in the atypical cases there are no clinical aids to the differentiation from the spasmodic and paroxysmal cough present in various catarrhal affections of the respiratory tract. As a result, the enforced policy of watchful waiting from a tentative diagnosis in the catarrhal stage to a more definite diagnosis in the paroxysmal stage is usually a definite factor in the spread of the disease.

While the cough plate has now assumed a definite place and is of definite value, nevertheless it is not always feasible in the absence of proper facilities; and even when these are available, the culture of the Bordet-Gengou bacillus is not always easily achieved, nor are the specimens received always entirely suitable for the purpose.

A. E. Gold and H. O. Bell (Am. J. Dis. Child. 52:25 (July) 1936), therefore, attempted to correlate the studies of various European investigators in the laboratory studies of whooping cough and, as a result, have proposed a new diagnostic triad characteristic of pertussis in the atypical and uncomplicated form of aid in the study of suspicious

conditions and in the absence of positive findings in cough plates.

The triad consists of a suspicious cough, a blood picture showing lymphocytosis in association with leukocytosis, and a retarded (normal or subnormal) sedimentation rate.

Absence of these findings does not invalidate the diagnosis of whooping cough, while their presence makes it definitely probable.

These conclusions were based upon careful and relatively extensive studies and the proposal seems worthy of the attention of the clinician.

**HEPATIC FUNCTION.**—The number of procedures proposed as indices of hepatic function is *ipso facto* evidence that the perfect liver function test has yet to be found.

L. J. Soffer and M. Paulson (Am. J. M. Sc. 192:535 (Oct.) 1936) regard the excretion of bilirubin injected intravenously as the most delicate and satisfactory procedure yet devised.

This procedure, first devised by Eilbot in Germany (1927), and first reported upon in the United States by Harrop and Barron (1931), has been modified by Soffer and Paulson, who carry it out as below described. These investigators believe that this test is the most sensitive yet described, and attribute its sensitivity to the following factors:

1. The excretory function of the liver is measured by its ability to handle a substance normally manufactured by the body and normally excreted by the liver.

2. In many instances the excretory function of the liver is the first to be disturbed, so that a physiological substance like bilirubin furnishes a logical index for appraisal.

3. The usual excretory tests for hepatic function are based upon the selective activity of the liver to remove foreign products such as dyes from the

circulation and excrete them into the duodenum. However, this is only true in part, as evidence exists to indicate that dyes such as bromsulphalein, when intravenously injected, are partly phagocytised by the reticulo-endothelial cells and hence not removed in entirety by the liver. Bilirubin, on the other hand, circulates freely and, except in obstructive jaundice, is excreted by the liver *in toto*.

It is true that in obstructive jaundice storage of bile pigment occurs in the reticulo-endothelial cells. This test, therefore, cannot be used in the presence of bilirubinemia in excess of 1 mgm. per cent.

**METHOD.**—1. A total of 1 mg. of bilirubin per kilogram ( $2\frac{1}{2}$  lbs.) of body weight (except that the dose should never exceed 70 mgs.) is dissolved in 15 c.c. of  $\frac{1}{10}$  molar solution\* of sodium carbonate which has previously been brought to the boiling point and then cooled to 80° C. Care should be taken to prevent overheating the carbonate solution to avoid reactions (nausea, hot flashes) from a too strongly alkaline reaction. The bilirubin dissolves completely, producing a clear iodine-colored solution.

2. With a *dry* syringe (to avoid hemolysis), collect a control sample of oxalated blood.

3. *With the needle in situ*, the bilirubin is then injected intravenously.

4. Oxalated blood samples are obtained from the other arm 5 minutes later and again 4 hours after the injection.

5. Bilirubin estimations are made by the method described by Z. Ernst and J. Förster (Klin. Wchnschr. 3:2386 (Dec. 23) 1924), the plasma being precipitated by redistilled acetone used in concentrations dependent upon the amount of bilirubin in the sample. Thus, with the 5-minute sample, 4 c.c. of acetone are added to 1 c.c. of plasma, while with the 4-hour sample, 2 c.c. of acetone are added to 2 c.c. of plasma.

6. After the plasma and acetone mixtures are shaken, they are centrifuged, filtered, and promptly matched against the standards. Except during actual readings, the acetone solution of bilirubin must be protected from light.

\*A molar solution is one containing 1 gram molecule per liter.

**Preparation of Standards.**—Prepare a 1:2000 solution of potassium dichromate which has a color equivalent to that of 1 mgm. per cent. of circulating bilirubin. From this a series of dilutions is prepared having the values shown below in milligrams per cent. of bilirubin:

|              |              |                |
|--------------|--------------|----------------|
| 1:2000 = 1.0 | 1:2857 = 0.7 | 1:5000 = 0.4   |
| 1:2222 = 0.9 | 1:3333 = 0.6 | 1:6666 = 0.3   |
| 1:2500 = 0.8 | 1:4000 = 0.5 | 1:10,000 = 0.2 |

**Calculation:**

A. (control)  $\times$  2 (dilution) =  $A^1$ .

B. (5-minute specimen)  $\times$  5 (dilution) =  $B^1$ .

C. (4-hour specimen)  $\times$  2 (dilution) =  $C^1$ .

Then:

$$\frac{C^1 - A^1}{B^1 - A^1} \times 100 = \text{percentage retention of bilirubin.}$$

**INTERPRETATION.**—Bilirubin retention in excess of 5 per cent. after 4 hours is considered abnormal and indicative of disturbance of hepatic function.

**CONTRAINDICATION.**—In the presence of hyperbilirubinemia, since it is obvious that the liver cannot handle adequately the bile pigment already present in the blood, the test cannot be used.

**PRECAUTIONS.**—Mention has already been made as to the necessity for avoidance of overheating of the carbonate solution to prevent reactions which, however, consist only of nausea and hot flashes and subside within a few minutes.

Proper care must be taken to inject the solution *intravenously*; should accidental extravasation occur, localized pain, edema and tenderness, and, rarely, pyrexia result. Sloughing does not occur and any constitutional reaction subsides without residue in 48 hours.

**UNDULANT FEVER. — Treatment.**—Despite the fact that undulant fever is now recognized as a wide-spread and fairly prevalent disease, methods for its treatment are still uncertain and somewhat unsatisfactory. The recent report of C. E. Ervin, H. F. Hunt, and J. S. Niles (Am. J. M. Sc. 192:234 (Aug.) 1936) upon the treatment of undulant fever by the intravenous injection of killed typhoid-paratyphoid "A" and "B" bacilli is of decided interest.

Their method consists of the intravenous administration of **mixed typhoid vaccine**, each cubic centimeter of which contains 1000 million typhoid bacilli and 500 million each of paratyphoid "A" and "B." The initial dose of 50 million killed organisms was repeated every 5 days, until 4 to 6 treatments have been given, the dosage being increased 25—50 million each time.

Ten of 12 cases treated with vaccine intravenously recovered quite promptly without recurrence or other sequelæ, and follow-up agglutination tests for *Br. abortus* were negative. While the series of cases is small, the results of the method were sufficiently striking to warrant its further trial by others. This method, of course, is simply a further application of foreign protein therapy.

**AMEBIASIS. — Diagnosis.** — The diagnosis of amebiasis is made primarily in the laboratory and, in large degree, depends upon the results of examination of direct smears, of fixed and stained preparations, and, within recent years, of cultures.

All of these procedures were used extensively in the study of the outbreak which occurred in Chicago during the World Fair and, as a result of this experience, W. DeYoung (J. Lab. and Clin. Med. 21:1149, 1936) presents an interesting and valuable report upon their fallacies and the errors which may be made in their use.

Obviously, in the laboratory study of amebiasis, the differentiation of *Endameba histolytica* from *Endameba coli* is of the greatest importance. That the latter may sometimes possess some of the characteristics of *Endameba histolytica* has been appreciated and commented upon by many workers; and that the identification of these two forms may sometimes be a matter of difficulty was emphasized by the Chicago survey.

This is particularly important because of the numerous conditions which may have a more or less clinical and symptomatic resemblance to amebiasis (non-specific ulcerative colitis, carcinoma of the colon, tuberculous enteritis, "functional colitis," milder types of bacillary dysentery, as well as other less common conditions), in which the finding of a few nonpathogenic amebæ, particularly *E. coli*, may prove misleading both as to treatment and prognosis.

The points emphasized by DeYoung may be summarized under several headings:

1. *Collection of Specimen.* — It is absolutely essential that the specimen be freshly obtained and, if loose, examined within 30 minutes. Refrigeration or incubation cannot be relied upon to guard against degeneration.

Specimens containing oil or obtained by oil catharsis, as well as those containing bismuth or arsenic crystals, are unsatisfactory for examination and such medication should be discontinued for one week prior to the examination. Indeed, whenever possible, all antiamebic drugs should be withheld until a sufficient number of examinations have been made either to confirm or rule out the diagnosis. A satisfactory examination should include 5 or 6 specimens, at least one of which should be secured by a *rectal tube* or proctoscopy.

If a barium enema has been given for radiographic purposes, at least 1 or 2 weeks must elapse before a satisfactory specimen can be secured.

Examinations are best confined to material from a natural bowel movement, although it is quite possible that a saline purge may increase the number of cases detected upon a single examination. But as *E. coli* tends to become quite active after a saline purge, this procedure may be a source of confusion.

2. *Direct Smear Examination*.—Although open to error, when proper precautions are observed this is one of the most reliable of available methods. Certain of the precautions advisable have been referred to under the collection of the specimen and others will be referred to below.

Slides should be wiped immediately before use, as crystals resembling bismuth may be found on "clean" slides.

In the direct smear the following forms may be encountered: cysts, trophozoites, precepts, and what have been spoken of as "inactive trophozoites."

When cysts of *E. histolytica* are found, the diagnosis of amebiasis may be considered definite.

Four-nucleated cysts of *E. coli* may be seen and may prove confusing, but a study of the nuclei and, with the iodine stain, the evenly coarsely granular cytoplasm of *E. coli* is of aid in the diagnosis. The inexperienced observer must be careful not to miss very small cysts of *E. histolytica* ranging in size from 6 to 7 microns.

While in the temperate zones but few cases are found showing typical trophozoites of *E. histolytica* containing ingested red cells, such trophozoites when found are diagnostic. The diagnosis is also justifiable where the trophozoites seen exhibit a majority of the accepted characteristics of *E. histolytica*. These characteristics, in the absence of ingested erythrocytes, are: clear, hyaline pseudopodia, either "exploding" or merely "crawling along a thin ectoplasmic wall"; rapid, progressive motility; clearly differentiated endoplasm and ectoplasm; a thin-walled, evenly granular, indistinct nucleus; and a cytoplasm in which yeasts, débris, or bacteria are but rarely seen.

Absence of any one of these characteristics throws considerable doubt on the diagnosis.

It must be remembered that, even under the best of conditions, the characteristics differentiating *E. histolytica* and *E. coli* are not marked. Indeed, Wenyon, in 1925, speaking of these forms and the Councilmania, said, "any single species may show all the variations which are supposed to characterize these several species."

3. *Diagnosis By Stained Smears*.—The staining of amebæ—and this is also true of the study of such smears—demands experience and patience. A reliable, though laborious, method is iron hematoxylin after fixation in hot Schaudinn's solutions.

The characteristics of the stained nuclei of amebæ are recited in detail in standard texts on protozoölogy and need not be repeated here, but it may be emphasized that the staining characteristics of nuclei of *cultured E. coli* and *E. histolytica* are not as clear-cut as in the nuclei of stool amebæ.

Examination by staining methods is indicated where the trophozoites seen in direct smears are sluggish or inactive.

Stained smears must be made from freshly secured specimens and, when these are loose, the staining must be carried out within 30 minutes.

In this connection, the method described by D. L. Sargent (Stain Technol. 11:49, 1936) for the staining of protozoa in the direct smear is of interest and claimed to be a definite improvement.

A portion of the fecal material to be examined is suspended in a 0.6 per cent. salt solution; the suspension should be of a consistency so that one drop will make a satisfactory microscope mount under a cover-glass. To 10 parts of this suspension, in a test tube, is added 1 part of the stain which is prepared as follows:

10 parts of distilled water.

6 parts of a suspension of colloidal iodine (Chandler) containing 4 per cent. iodine—20 per cent. iodine suspensoid, Merck.

1 part of a 10 per cent. water solution of anilin red, Merck (eosin yellowish).

Because iodine in the form of colloidal iodine is readily released to the organisms, this material is far superior to Lugol's solution in carrying out the technic for staining intestinal protozoa in the study of fresh mount preparations. Not only are organisms more deeply stained with iodine, but by eosin as well, even when employed in high dilutions.

4. *Examination By Culture*.—This method, introduced in 1925, has since been modified and the culture medium improved by many workers, among them Cleveland and Collier, whose medium (liver-infusion-agar to which rice starch is added) was used by DeYoung.

There have been many comparative studies of the value of cultures and direct smear examination from which varying conclusions have been derived, but it must be recognized that such conclusions are influenced by several factors. (a) The number of smears examined from a single sample and the time spent on each; (b) the skill and experience of the observer; and (c) the fact that *E. coli* and *E. histolytica* cannot always be differentiated in culture, as "the two species are extremely alike in cultures." (Dobell and Laidlaw.)

From his experience, DeYoung concludes that, particularly in surveys, the use of primary cultures may be a source of error and, for that reason, should not be used as a means to a final diagnosis.

**DINITROPHENOL DETECTION.**—*In Blood and Urine*.—Despite the reports illustrating the toxic and even fatal effects of a-dinitrophenol, its recent use in the treatment of obesity has already been followed by its indiscriminate use by the laity without medical supervision. It has also, openly or secretly, been incorporated in the propri-

etary products sold for the self-treatment of obesity.

The tests devised and described by A. Bolliger (M. J. Australia 1:367 (Mar. 17) 1934) for its detection in urine and blood are applicable to cases of suspected poisoning with this drug:

The tests are based upon the fact that 2:4 dinitrophenol forms very readily with methylene blue an addition compound similar to that formed by picric acid. By simply adding a solution of methylene blue to a solution of dinitrophenol-methylene blue, dinitrophenolate is obtained, which crystallizes in fine bronze-colored needles. This compound is sparingly soluble in most solvents to form a green solution. Its solubility in chloroform is greater, but considerably less than that of the corresponding picrate. The practical application of this reaction in the detection of a-dinitrophenol is as follows: The acidified solution is extracted with chloroform and to the neutralized chloroform extract a dilute solution of methylene blue is added. If dinitrophenol or a similar compound is present, the chloroform extract will become green.

The methods follow:

**URINE.**—In a separating funnel a volume of urine (20 c.c., if available) is acidified with one-tenth of a volume of 70 per cent. sulphuric acid. It is then extracted by gentle shaking for about 3 minutes with half its volume again of chloroform. If possible, permanent emulsions have to be avoided. However, if after some standing sufficient chloroform does not separate out cleanly, it must be separated by centrifugation. Then about 10 c.c. of the chloroform extract are transferred to a test tube containing a gram or so of calcium carbonate. The contents are mixed well and 0.0001 N methylene blue, chemically pure (about 0.004 per cent.) is added in very small drops.

The mixture is well shaken after every drop until the first change of color of the contents occurs. It is then filtered through a dry filter into another test tube; an equal amount of distilled water is added; it is shaken well

again and the water is removed. If the chloroform shows a distinct green color which cannot be extracted by further washings with water, a-dinitrophenol is present in the urine. If there is any doubt, some of the chloroform extract may be concentrated by evaporation in order to intensify the color.

If dealing with amounts of dinitrophenol up to 1 mg. per cent. in urine, the application of the precautions mentioned will be necessary, because some substance present in normal urine in small amounts and extracted by chloroform seems to form with an excess of methylene blue a bluish compound, which may easily be misleading. Therefore, for the detection an excess of methylene blue has to be avoided. But after the presence of dinitrophenol has been established by the typical greenish color of the chloroform extract, more methylene blue may be added either to get an approximate idea of the amount of the drug present or to perform an actual quantitative estimation by the technic which will be described below. Doubtful results with regard to the presence or absence of the drug may be compared with those obtained with urine treated similarly, which are known to contain no dinitrophenol. With amounts above 1 mg. per cent., the results are beyond doubt.

**BLOOD.**—Serum acidified with a few drops of sulphuric acid is thoroughly shaken with an equal amount of chloroform. The mixture is then centrifuged and the chloroform extract pipetted off and filtered through a dry filter into a test tube containing some calcium carbonate. Then 0.0001 N methylene blue is added in small drops until the mixture begins to change color. After filtering again, the presence of dinitrophenol is indicated by a green tint of the chloroform extract.

**SOLUTIONS.**—A known amount is dissolved in 5 per cent. sodium hydroxide. After the solution is acidified with 70 per cent. sulphuric acid, the dinitrophenol is extracted with several lots of chloroform. The combined chloroform extracts are treated with calcium carbonate, filtered and made up to a known amount. An aliquot part of the chloroform extract is transferred to a separating funnel and 0.0001 N methylene blue is added from a burette. The methylene blue combines with the dinitrophenol to the chloroform-soluble methylene blue dinitrophenolate. Therefore, on extraction the watery layer originally containing the methylene blue turns yellow, while the chloroform takes on a green color. The end point is reached when the watery layer

becomes colorless. For practical reasons, the appearance of the first tint of blue which cannot be extracted with fresh chloroform is regarded as the end point. In other words, when a definite end point has been reached, the dark green chloroform must be discarded and the watery layer must be extracted with fresh chloroform. It will then usually be found that the end point has not yet been reached and more methylene blue has to be added, followed by further extraction with fresh chloroform. As already mentioned, the solubility of the methylene blue dinitrophenolate in chloroform is comparatively slight and it is practicable only for amounts up to about 10 mg. of dinitrophenol to be determined by this procedure. If dealing with larger amounts, it is recommended to precipitate all of the dinitrophenol with a small excess of 0.01 N methylene blue and to determine the excess of methylene blue, as described in a previous publication (Proc. Roy. Soc. New South Wales 67: 240, 1933).

As already mentioned, the test described is not specific for 2:4 dinitrophenol. A similar compound is given by 2:4:6 trinitrophenol (picric acid), and this could be differentiated from the dinitro compound by the considerably greater solubility in chloroform. In general, it seems that all polynitro derivatives of phenol and naphthol with a nitro group in orthoposition to the hydroxyl group form with methylene blue an addition product which dissolves in chloroform with a green color.

**BLASTOMYCETES.—Detection of.**—The following method for the detection of blastomycetes is described by R. Nomland (Arch. Dermat. and Syph. 32: 924 (Dec.) 1935):

A micro-abscess in the sloping border of the skin is pierced and the pus picked up on the point of a sharp knife. It is then transferred to a slide and mixed with a small amount of tap water; a cover-glass is pressed on and the material examined with the iris diaphragm on the Abbe condenser almost closed.

Water is superior to solutions of sodium hydroxide because water does not form artefacts such as are made by the interaction of sodium hydroxide and fats in the specimen..

**SKIN FUNGI.—Direct Microscopical Examinations.**—J. H. Schwartz and N. F. Conant (*Ibid.* 33:291 (Feb.) 1936) have found that the treatment of scrapings from the skin with 5 per cent. potassium hydroxide, followed by washing with water and staining in lactophenol and cotton blue, makes possible the easy determination of the presence of fungi. This method of preparing microscopic specimens for examination is simple in that it adds only two steps to the more common method using potassium hydroxide, and is effective in that the fungi are definitely stained while the various confusing artefacts are eliminated from the picture.

This is particularly true of the mosaic growth which occurs commonly in preparations made with potassium hydroxide. This material does not seem to be the result of treatment with potassium hydroxide, since it can be found in scales treated with xylene or with chloral hydrate and acacia. It was found to be soluble in ether, 95 per cent. alcohol, absolute alcohol, and phenol. It could not be stained with sudan III or scarlet red or blackened with osmic acid. While fungi were readily stained with lactophenol and cotton blue, mosaic material which occurred in the same preparation did not stain and was, in fact, entirely eliminated. In presence of polarized light there was no evidence that mosaic material was composed of crystalloid forms.

Whatever the nature of the mosaic growth, these workers feel that they have presented sufficient proof that it is not a fungus. The staining of normal fungi in scales with lactophenol and cotton blue, the failure to find partially degenerated forms in the same preparation in which both mosaic material and fungi occurred, and the failure to find morphologic connections between normal hyphæ and these mosaic forms, seem to disprove convincingly the theory

that this material is a degenerate form of fungus.

The method follows:

*Reagent:*

|                                |        |
|--------------------------------|--------|
| <i>Lactic acid</i> .....       | 1 c.c. |
| <i>Phenol crystals</i> .....   | 1 Gm.  |
| <i>Glycerin</i> .....          | 2 c.c. |
| <i>Water (distilled)</i> ..... | 1 c.c. |

To this may be added 0.5 per cent. cotton blue (C4B Poirrier), which was considered by Langeron to be the best type.

When scales were gently heated in a drop of this liquid on a slide and a cover-glass was pressed on them, it was seen that fungi, when present, stained more deeply than did the epidermal cells. The varied thicknesses of the scales, however, hampered the effectiveness of the clearing action of the lactophenol, and it was found advantageous to subject the scales to preliminary clearing in a 5 per cent. solution of potassium hydroxide. After this preliminary treatment, the scales were transferred to a watch crystal and washed with water. When the action of the potassium hydroxide was stopped after 2 or 3 minutes of washing, the scales were gently heated in a drop of the lactophenol-cotton blue mixture, and a cover-glass was pressed on the preparation. The clearing action of the potassium hydroxide was continued by the lactophenol, and the epidermal cells received a light bluish stain, while the granular protoplasmic content of the fungus was heavily stained. It was noted, however, that in some thick preparations the fungus was visible but slightly stained. These scales, after being treated in 5 per cent. potassium hydroxide and washed in water, were stained with cotton blue in 70 per cent. alcohol (1 per cent. solution). They were then mounted in clear lactophenol and the preparation was pressed out under a cover-glass. The fungi were heavily stained, showing the protoplasmic content and hyaline outer sheath.

To obtain permanent preparations of the scales stained with lactophenol and cotton blue, all that is necessary is to wipe off the excess medium around the cover-glass and cement the cover to the slide with Noyer's cement. Another method of obtaining permanent preparations was found to be that of mounting the stained scale in chloral hydrate and acacia. The formula follows:

|                              |         |
|------------------------------|---------|
| <i>Distilled water</i> ..... | 50 c.c. |
| <i>Chloral hydrate</i> ..... | 50 Gm.  |
| <i>Glycerine</i> .....       | 20 c.c. |
| <i>Acacia</i> .....          | 30 Gm.  |



**TRICHOMONAS.—Contrast Stain.**—The procedure described by J. R. Miller (J. A. M. A. 106:616 (Feb. 22) 1936) is of use in the detection of *trichomonas vaginalis*. It consists merely of the use of a drop of 0.1 per cent. safranin, used as a diluent for the pus to be examined.

Not only the nuclear material, but protoplasm also of the leukocytes rapidly takes safranin stain, whereas the *Trichomonas vaginalis* organism remains unstained and conspicuous as a clear object against a slightly pink background.

It is noticeable also that the safranin, at least in this dilution, does not interfere with the motility shown by *Trichomonas*; if anything, it appears to stimulate it. Under the low power it is often possible to pick out more quickly areas where the organisms are numerous, so that identification with the high power objective can be quickly effected.

**BREAST MILK.**—A constant supply of sterile expressed breast milk is of great value for the emergency requirements of a feeding service in a pediatric hospital.

A method for the preservation of breast milk and its clinical use is described by L. A. Scheuer and J. E. Duncan (Am. J. Dis. Child. 51:249 (Feb.) 1936).

Over a period of 2 years, bacteriological examinations of the specially pasteurized breast milk showed that it remains sterile. Chemical analysis at the end of the second year showed similar values for the specially pasteurized milk and for fresh breast milk.

Examination of the stools of the infants fed the specially pasteurized breast milk showed the fecal flora to be the same as that of the infants fed fresh breast milk.

The method follows:

Seven ounces (178 c.c.) of unpasteurized breast milk and  $\frac{1}{2}$  ounce of sterile water are placed in each of a number of ordinary 8-ounce (236 c.c.) formula bottles. Sterile corks are then placed in the bottles but not pushed down tightly, as they would blow out when the milk is heated. Over each of the corks are placed 6 layers of sterile gauze, a large piece of cotton, and, finally, a piece of paper. This covering is secured by means of a large rubber band. The bottles are then placed in a bottle rack of 8 sections and the rack placed in the top of a double boiler in cold water which reaches to the level of the milk in the bottles. The water is maintained at a temperature of 175° F. for 30 minutes. The bottles are then kept for 24 hours at room temperature. At the end of this time the process is repeated, and again at the end of 48 hours. Following the third heating, the corks are tightened in the bottles, the coverings of the corks removed, and the corks sealed with paraffin. Finally, the bottles are stored in the refrigerator at a temperature of 38° F. to 52° F.

## THERAPEUTICS, GENERAL

By EDWARD A. MULLEN, PH.D., M.D.

**ACETARSONE (STOVAR-SOL).—Indications and Dose.**—The use of arsenicals in the treatment of *Vincent's angina*, has long been advocated. C. H. Maxwell, Jr. (New York State J. Med. 36:874 (June 1) 1936), recommends the use of acetarsone for treatment in the following doses:

| Age                            | First Day                          | Second and Third Day               |
|--------------------------------|------------------------------------|------------------------------------|
| Adults (Patients 12 and above) | 0.125 Gm. (2 grains) 4 times daily | 0.25 Gm. (4 grains) 3 times daily  |
| 8 years. . . . .               | 0.125 Gm. (2 grains) 3 times daily | 0.125 Gm. (2 grains) 4 times daily |
| 4 years. . . . .               | 0.0625 Gm. (1 grain) 3 times daily | 0.125 Gm. (2 grains) 3 times daily |
| Infants. . . . .               | 0.0625 Gm. (1 grain)               | 0.0625 Gm. (1 grain) 3 times daily |

This dosage may seem large, since the drug is not without its dangers, as reported by C. H. Maxwell, Jr., and J. Glaser (Am. J. Dis. Child 43:1461 (June) 1932), but smaller doses used at the onset do not give rapid results.

It is given by ingestion or made into a paste and gently massaged into the gums, the patients being encouraged to swallow all of the drug. In small children, it is applied with a cotton swab.

The most dramatic results were obtained in 24 hours. In the majority of ten cases, they were able to eat without difficulty according to Maxwell (*Ibid.*), (898)

who recommends acetarsone as a satisfactory arsenical for the treatment of *Vincent's angina* and *stomatitis*. Concurrent local application and ingestion of the drug are suggested.

In *congenital syphilis*, the ease of administration of acetarsone has proved its value over previous forms of treatment.

The dosage as recommended by A. Bratusch-Marrain (Arch. f. Kinderh. 92:26 (Nov. 28) 1930) consists of graduated doses in proportion to the weight; 5 mg. ( $\frac{1}{12}$  grain) of the drug per kilogram ( $2\frac{1}{5}$  pounds) of body weight are given daily for one week, followed by 10 mg. ( $\frac{1}{6}$  grain) per kilogram the second week, 15 mg. ( $\frac{1}{4}$  grain) per kilogram the third week, and 20 mg. ( $\frac{1}{3}$  grain) per kilogram the fourth week, and so on until the ninth week. This is followed by a 6-weeks' rest period, when the course is repeated, irrespective of the serological reaction.

A. M. Davidson and A. R. Birt (Canad. M. A. J. 34:33 (Jan.) 1936), as a result of its use in 51 cases over a period of 4 years, believe that stovarsol is superior to the older methods of treatment. The decided increase in the percentage of cases cured is enough in itself to assure this drug a permanent place in the therapy of *congenital syphilis*. It offers the following advantages over other forms of treatment:

1. **Simplicity of Exhibition.**—The oral method is much superior to the intravenous or the intramuscular route in children, for obvious reasons.

2. **Regular Attendance at Clinic.**—Syphilis in all its forms can only be cured by regular treatment. Regular

attendance of children at the clinic was by force.

3. Toxic Effects.—There have been fewer toxic effects in this series than are usually found with arsphenamine and neoarsphenamine. Those which have been produced were readily controlled by dosage.

4. Cost.—The treatment is much cheaper. The stovarsol costs less and no additional equipment is necessary for administration.

In the course of treatment, 3 patients had mild toxic symptoms.

The stovarsol tablet is 0.25 Gm. (4 grains) by weight and is large enough to be readily cut into four parts. For infants it was dissolved in water or in part of the milk feeding.

#### *Dosage*

- $\frac{1}{4}$  tablet once a day for 1 week.
- $\frac{1}{4}$  tablet twice a day for 1 week.
- $\frac{1}{4}$  tablet 3 times a day for 1 week.
- $\frac{1}{4}$  tablet 4 times a day for 1 week.
- $\frac{1}{2}$  tablet 3 times a day for 1 week.
- $\frac{1}{2}$  tablet 4 times a day for 1 week.
- 1 tablet twice a day for 1 week.

Total: 56 tablets (14 Gm.— $3\frac{1}{2}$  drams) in 49 days, followed by a 6-weeks' rest period.

**Untoward Effects.**—The toxic manifestations, according to H. S. Mitchell (Canad. M. A. J. 33:377 (Oct. 1935), are diarrhea and vomiting, which are two of the earliest symptoms of intolerance or intoxication. Febrile disturbances occur occasionally. Mild or moderate albuminuria may arise either independently or in conjunction with other signs of intoxication. Arsenical dermatitis occasionally develops. Neuritis or myelitis are among the more serious hazards, and must be constantly watched for. Seven deaths occurring in children under treatment with stovarsol have been reported. Caution is emphasized in the administration of the drug, and in the supervision of the patients while under treatment.

### ACETYLSALICYLIC ACID.—

**Poisoning.**—Poisoning by acetylsalicylic acid may be delayed for a few hours and manifest itself first by disturbance of the nervous system. Dissolution in 12 hours or more may take place as a result of profound cerebral depression, according to A. W. Neale (Brit. M. J. 1:109 (Jan. 18) 1936). Gastrointestinal irritation with vomiting may be absent. Disturbance of heat regulation occurs, and profuse sweating may be regarded as an important clinical sign. Dehydration which is associated, portends the toxic effect of the drug. Auditory and vestibular disturbances are noted in some cases. The *diagnosis* is based on the patient's mental state, the presence of severe perspiration and respiratory changes, also the examination of the urine for the presence of salicylic acid. The dangerous dose of acetylsalicylic acid is 400 to 500 grains (26 to 32 Gm.).

In the *treatment*, Neale recommends combating dehydration by **enteral fluids** or continuous intravenous drip of **dextrose-saline solution**, and by **lumbar puncture** (cerebrospinal fluid contains the drug in considerable amounts).

N. Francis, O. T. Ghent and S. S. Bullen (J. Allergy 6:504 (July) 1935) give a report of death in an asthmatic patient from the ingestion of 10 grains (0.6 Gm.) of acid acetylsalicylic acid (aspirin).

### ALCOHOL.—*Physiological Action.*—

The ability of alcohol to destroy the protolytic enzymes of gastric juice has long been taught, and is proven by H. Blotner (J. A. M. A. 106:1970 (June 6) 1936), through a series of experiments on gastric juice mixed with alcohol. Specimens of gastric juice were also obtained from known alcoholics, which showed that a sufficient amount of alcohol inhibits the protolytic activity of certain gastrointestinal en-

zymes and that large quantities of alcoholic liquor taken over a long period of time destroy digestive enzymes and prevent the proper digestion and assimilation of food.

**ALOE.**—*Therapeutics.*—S. Wright (J. A. M. A. 106:1363 (Apr. 18) 1936) scraped out the intestinal contents of the aloe vera leaf, which contains a large quantity of light yellowish green material having about the color and consistency of lemon jello, and mixed it with an equal quantity of aquaphor. The patient was instructed to massage this into the skin every night.

Remarkable improvement was obtained in 2 cases of *x-ray telangiectasia* resulting from ill-advised attempts at x-ray depilation.

In view of the unfortunate but nevertheless occasional burns that may result from over-exposure to x-rays, any therapeutic agent that offers a hope of quick healing and relief of discomfort in such sequelæ is worthy of further study. The permanence of results can be determined only by watching cases thus treated over a period of time.

#### **ALUMINUM HYDROXIDE.**—

*Therapeutics.*—The effect of aluminum hydroxide used in the treatment of *peptic ulcer* on the gastric acidity and blood chemistry was studied by W. L. Adams, I. H. Einsel and V. C. Myers (Am. J. Digest. Dis. and Nutrition 3:112 (Apr. 1936)).

By the use of a colloidal aluminum hydroxide cream in doses of 1 dram (4 c.c.) 6 times a day, burning, nausea and pain were markedly relieved within a few days in 125 cases of peptic ulcer. Food could be taken without distress and weight gradually returned.

They found in 7 cases by repeated blood and gastric analyses, that there was a decrease in the total amount of

acid and of the free acid in the gastric secretion 90 minutes after the administration of the drug. If the dosage was reduced, there was a tendency toward increase in the gastric acidity, indicating no permanent damage to the secreting mechanism. No significant blood changes were noted and the minor changes that were demonstrated showed a tendency of the blood chloride to rise and carbon dioxide to fall, *i. e.*, away from alkalosis.

The authors conclude that colloidal aluminum hydroxide is the most satisfactory antacid thus far employed.

These results are concurred by E. E. Woldman and V. C. Rowland (Rev. Gastroenterol. 3:27 (Mar.) 1936), who use a continuous 24-hour drip of a 7 per cent. colloidal suspension of aluminum hydroxide. They emphasize the freedom from the danger of alkalosis and secondary acid secretions.

#### **AMMONIUM CHLORIDE.**—

*Untoward Effects.*—G. D. Oppenheimer (J. Urol. 33:22 (Jan.) 1935) calls attention to the fact that in urological cases where renal function may be reduced, the possibility of acidosis must be kept in mind when acidifying salts are administered.

Ammonium chloride is decomposed into ammonia and hydrochloric acid. Ammonia is converted into urea and excreted by the kidneys, while the hydrochloric acid is neutralized in the blood at the expense of alkalis; with large doses, therefore, acidosis results. The *treatment* is **immediate withdrawal** of the drug, large doses of **sodium bicarbonate** by mouth or rectum, and intravenous injection of 5 per cent. solution of **glucose**.

**AMMONIUM PHOSPHATE ACID.**—*Physiological Action.*—The pH of the urine has been a subject of recent discussion and a variety of drugs

have been used to increase its acidity. S. Alstead (Edinburgh M. J. 43:292 (May) 1936) states that acid ammonium phosphate used in doses of 30 grains (2 Gm.) 3 times a day markedly diminished the pH of the urine, and no further increase in the hydrogen ion concentration occurred with greater doses. The saline cathartic action was noted when the daily dose reaches  $4\frac{1}{2}$  drams (17 Gm.), *i. e.*, 3 times the effective dose for acidifying the urine. He also states that acid sodium phosphate is of negligible value as an acidifier of the urine. Frequently, it actually alkalizes the urine.

#### ANTIDOTUM METALLORUM.

—A new antidote against toxic heavy metals, as prescribed by C. Strzyzowski (Presse méd. 44:780 (May 13) 1936), is **hydrogen sulphide**.

The method of preparation is as follows:

Two liters of distilled water are heated to boiling. Two grams (30 grains) of **sodium hydroxide** are dissolved in half of this water and it is then supersaturated until cold by a current of **hydrogen sulphide** previously washed by being passed through a suspension of calcium carbonated water. Meanwhile, when the remaining water reaches a temperature of 50° C., 7.5 Gm. ( $1\frac{9}{10}$  drams) of crystallized **magnesium sulphate** and 25 Gm. ( $6\frac{1}{4}$  drams) of **sodium bicarbonate** are dissolved in it. When cool, this second solution is added to the first and mixed, after having been cooled to 2 or 3° below zero, and finally saturated at this temperature with hydrogen sulphide gas. The preparation is placed in 125 c.c. flacons, sterilized, and cooled to as close to zero as possible. They are then stoppered with red rubber of good quality and sealed with paraffin. As prepared, the antidote is colorless at first, but later develops a slight yellow tint, which is an index of its good quality.

One hundred c.c. ( $3\frac{1}{3}$  ounces) of this antidote recently prepared can instantly convert 4 Gm. (1 dram) of mercury bichloride into inactive sulphur of mercury. The preparation is quite stable

and the author believes that it is effective for detoxification of a large number of heavy metals, such as *antimony, cobalt, iron, mercury and lead*.

**ARSENIC.—Poisoning.—ETIOLOGY.**—The sources of many cases of chronic arsenical poisoning, still remain undetermined. A. B. Cannon (New York State J. Med. 36:219 (Feb. 15) 1936) studied 107 cases exclusive of arsphenamine and treated syphilitics. In all cases laboratory tests of both urine and blood were made, using 71 healthy persons as controls. In a few cases, the arsenical dermatitis followed definite arsenical medication. More numerous were those cases in which the dermatosis antedated the medication, resulting in aggravation. Also, there were those cases in which the patient had not to his knowledge taken any preparation containing arsenic. The occupations of this group consisted of: 1 fruit grower, 1 grocer, 1 fruit peddler, (handling and eating sprayed fruits), 3 physicians, 1 nurse, and 1 manufacturer of cosmetics, all of whom had handled arsenic in the course of their work. There was also 1 candy worker (arsenic has been found as an impurity of commercial glucose, and occurs in shellac used as a coating for candies and in the colored paper used as wrappers for candies), 2 furriers (arsenic is in the dyes and disinfectant of furs), and 12 cases revealed contact with paints, colored wallpapers or household insecticides.

Arsenical poisoning in industrial workers from paints, enamels, metals and by-products has long been a matter of common knowledge, but it is less generally known that arsenic present in colored wall papers, wall paints, hangings and household objects may be toxic for occupants of rooms containing such furnishings (3 such instances in author's

file). Sprayed fruits were responsible in 3 cases.

Arsenic has been found by reputable investigators not only in fruits and vegetables, but in practically every item of human dietary.

The effects of arsenic may vary somewhat, depending on whether it is ingested, inhaled, or absorbed through the external skin. By any and all routes, it is capable of producing systemic poisoning, as well as local symptoms.

**DIAGNOSIS.**—Cannon (*Ibid.*) emphasizes the following practical consideration in regard to chronic arsenical poisoning: "Even the most typical symptoms are easily mistaken for other conditions; the gastroenteritis of the acute stage has frequently passed for ptomaine poisoning; the nose and throat symptoms for influenza and syphilis; the pigmentation for Addison's disease; and the cutaneous eruptions for everything from measles to erysipelas."

Every eruption or pigmentary disturbance that cannot be definitely identified by supporting evidence as due to other causes should be open to suspicion as a manifestation of arsenical poisoning.

Concerning opportunities for the intake of arsenic, the possibility of arsenical poisoning, should not be dismissed merely because a history of arsenical medication or exposure to some other known source cannot be established. Under present-day living conditions, it would be infinitely more difficult to prove that a patient has not been exposed to arsenic. A careful study of the patient's habits and environment and analysis of foods will often be necessary in order to establish the chronology of exposure and onset.

The *examination of the blood and urine* for arsenic is important not only to establish a diagnosis, but also to determine the fate of arsenic in the

human system and what may be considered the "limits of normal arsenic."

**TREATMENT.**—**Sodium** or **calcium thiosulphate**, either by injection or by mouth or both, hastens the excretion of such arsenic as may be stored up in the system. This method of treatment has also been found of value by H. G. Irvine and D. D. Turnacliffe (*Arch. Dermat. and Syph.*) 33:306 (Feb.) 1936), who used sodium thiosulphate, orally and intravenously, in 19 cases of arsenical dermatitis developed in industrial workers.

**ARSPHENAMINE.**—*Untoward Effects.*—In the review of deaths caused from arspenamine by S. S. Cook, (*U. S. Pub. Health Rev.*) 51:927 (July 10) 1936), 63 deaths are recorded in the United States Navy records for a period of 17 years from 1919 to 1935. All the patients had syphilis. The duration of infection in 21 was less than 6 months, and in 17 cases it was over 6 months. The time interval between the final injection and the onset of symptoms was less than 6 hours in 18 cases; over 6 hours in 20 cases. Neoarsphenamine caused the largest number (34) of the deaths, which was to be expected, as this is the arsenical most extensively used in the Navy.

None of the patients died after the first injection; 12 died after the second; 23 after 5 injections or less; 28 in more than 6 injections. In 44 autopsies performed, the striking findings were frequent hemorrhages and edema in the various organs of the body.

**BARBITAL.**—*Poisoning.*—A case is reported by D. K. Chang and M. L. Tainter (*J. A. M. A.* 106:1386 (Apr. 18) 1936) of the recovery of a patient who had ingested thirty-six  $7\frac{1}{4}$  grain tablets of sodium barbitol, a total dose of 270 grains, (18 Gm.).

The principal symptoms were deep coma, sluggish reflexes, increased respiration, rapid pulse and elevated temperature. Return of consciousness occurred on the fourth day, the coma lasting 6 days.

The *treatment* consisted of supportive measures. One liter (quart) of 5 per cent. **dextrose solution** was given intravenously, and 2 liters (2 quarts) of **physiological salt solution** by hypodermoclysis each 24 hours. **Caffeine**,  $7\frac{1}{2}$  grains (0.5 Gm.), was injected subcutaneously every 4 hours. The extremely high temperature was treated by **tepid sponge baths** and **ice-packs** combined with **frequent catheterization**.

**BENZEDRINE. — Physiological Action.**—The blood-pressure was found to fluctuate with the dose of 20 mg. ( $\frac{1}{3}$  grain) of benzedrine by S. A. Peoples and E. Guttmann (Lancet 1: 1107 (May 16) 1936). There was no blushing or pallor and no alteration of the size of the pupil, gastrointestinal motility, perspiration or genitourinary function. In blood sugar readings which were made during the experiment, there was no fluctuation beyond the normal limits. About one-quarter of the subjects reported dryness of the mouth. The latent period after the administration of the drug lay between 45 minutes and 2 hours; but once the action on the blood-pressure had become apparent, the maximal point was reached in about an hour. The normal pressure was reached between 2 and 5 hours after the peak, according to the dose given. The pressure changes were chiefly systolic, the diastolic showing little or no increase, so that there was an increase of the pulse pressure.

The majority of the subjects found difficulty in going to sleep and woke much earlier than usual. The first

psychic symptom after the administration of the drug was talkativeness, especially in depressive patients. The most interesting feature was a change of mood expressed in nearly every case. The change was generally in the direction of euphoria.

The authors conclude that the drug is promising for the treatment of psychic cases, but it cannot be used until it is known whether permanent administration produces anything like adaptation, habituation, or addiction.

**Therapeutics.**—Benzedrine was used in the treatment of 9 cases of *narcolepsy*, and gave complete relief from attacks of sleep and practically relief of cataplexy. M. Prinzmetal and W. Bloomberg (J. A. M. A. 105:2051 (Dec. 21) 1935) found that the drug had a profound stimulating action on the higher centers of the central nervous system. Comparative studies indicate that benzedrine is about 3 times as effective as ephedrine in preventing attacks of sleep in narcolepsy. In some cases, it gives complete relief from symptoms that are not relieved by huge doses of ephedrine. The dose used was 10 mg. ( $\frac{1}{6}$  grain) of benzedrine, 3 times a day. Untoward symptoms were observed, the patient being unable to sleep at night and an occasional case showed inability to relax. Reduction of the dose resulted in the disappearance of the symptoms. There is some individual variation in response to benzedrine.

**BROMIDES. — Untoward Effects.**—Reports of unfavorable results from the constant use of bromides continue to accumulate.

P. W. Preu, J. Romano and W. T. Brown (New England J. Med. 214:56 (Jan. 9) 1936) record 9 cases of bromide intoxication in the course of treatment of psychotic states. In 8 of these cases, deficient diet and dehydration

seemed to be definitely concerned in the onset of poisoning, and the authors believe that sufficient importance is not yet attached to this possibility. They insist that bromides must not be administered for long unless an adequate intake of fluids and chloride is maintained, and that a careful watch must be kept for symptoms of commencing toxicosis. The occurrence of a skin eruption is an unreliable criterion.

Bromides should never be used in cases of delirium due to toxic or infectious causes and should be administered with caution in arteriosclerosis, since delirium is easily thus induced if there is cerebral arteriosclerosis. For the *elimination of poison* which is determined by blood analysis, the authors used a **high caloric diet**, rich in **vitamins** and a minimum of 4000 c.c. (4 quarts) of **fluids** daily, with about 10 Gm. (2½ drams) of **chloride** in addition to the salt in the ordinary diet.

Alcoholism, beginning dementia paralytica, various toxic states, cerebral arteriosclerosis and general debility are predisposing to bromide intoxication, according to A. C. Kingsley (Southwestern Med. 20:170 (May) 1936).

High concentrations may be found even after its discontinuance, because ingestion of large amounts extended over a long period; 200 mg. soon after its discontinuance means far less than 25 mg. from a month to 6 weeks later. The general opinion is that it is safe to discontinue the drug suddenly. **Thorough elimination** should be established and **proper nourishment, fluids**, and **sodium chloride** from 12 to 16 Gm. (3 to 4 drams) daily, should be given. About 1 Gm. (15 grains) of sodium chloride neutralizes 5.8 Gm. (1½ drams) of bromides.

**CALCIUM.**—In recent years the therapeutic effect of calcium has been

studied more and more. It is generally accepted that the maintenance of calcium equilibrium in the tissues is of primary importance, not only for the adolescent but for adults as well. Practically all of the tissues of the body contain some calcium and the stores of calcium are constantly moving from place to place and undergoing modification according to the needs of the body. Ordinarily, the majority of the calcium is fixed in the bones and amounts to approximately 21 pounds. There is about one-third of an ounce distributed through the other tissues. It can therefore be seen that calcium exists in two different compounds in the body, *i. e.*, (1) as an insoluble preparation in bone, and (2) as a calcium preparation in the colloidal state which enters into the constitution of colloidal media of cellular metabolism.

Calcium has been found to exercise a tonic action on the heart muscle of great value. It plays a rôle in the conductivity of the nervous impulses, has some action on the sympathetic and parasympathetic systems; increases the activity of hormones; and has an influence on blood coagulation.

General health and recovery from disease are improved when an optimum supply and utilization of calcium are secured.

From this, it may well be understood why so many calcium preparations are used therapeutically today.

**Therapeutics.**—In *infantile convulsions*, when either present or threatening, an emergency treatment is used by W. R. Shannon (Journal Lancet 56:278 (May) 1936). He uses calcium intravenously and by intramuscular injection, supplemented by the injection of **parathyroid extract**. In discussion, he says the "essential symptomatology of all seizures is so like in character as to suggest with stubborn insistence that the underlying disturbance in cerebrocellular



function is similar, or essentially similar in all."

*Calcium chloride* or *calcium gluconate* may be employed for intravenous injection; calcium gluconate is used only for intramuscular injection. The intramuscular injection is slower but more sustained. The injection of the parathyroid extract, in addition to calcium, has proved a valuable procedure in the control of convulsions, as it also prolongs the effect of the injection. The parathyroid is used in doses of 0.75 to 1.25 c.c. (12 to 20 minims) for newborn infants, and for older infants, 1.5 to 2 c.c. (24 to 32 minims). This dose may be repeated at 4- to 8-hour intervals as long as nervous irritability and danger of convulsions exist. This is followed by the oral administration of calcium, such as *dicalcium phosphate*, *calcium gluconate* or *calcium lactate*.

**Dicalcium**, 2 grains (0.13 Gm.); **phenobarbital**,  $1\frac{1}{2}$  grains (0.1 Gm.); and **acetylsalicylic acid**, 5 grains (0.3 Gm.) was found by C. C. Robinson (Indiana M. A. J. 28: 662 (Dec.) 1935) to exert a very definite effect in *traumatic cases* in which hypnosis or sedation were required.

In pregnancy there is an extraordinary demand on the calcium of the mother for the needs of the growing fetus. Most investigators have found a low blood calcium in the late *toxemias of pregnancy* and it must be remembered that there may be actual calcium deficiency before the blood calcium becomes reduced, the calcium storage in various organs being depleted first. In the treatment of these late *toxemias*, A. A. Landry (New Orleans M. and S. J. 88: 567 (Mar.) 1936) recommends the use of **calcium** and **dextrose**.

Calcium can be supplied by diet and the administration of calcium salts, but to ensure its proper utilization, the ad-

ministration of **vitamin D** or **parathormone** is also necessary. He advises that in the later months of pregnancy **calcium** and **viosterol** should be given as a *prophylactic*, to patients showing minor symptoms, such as tingling in the hands and arms, legs and occasional cramps. This will give ultimate relief and prevents the development of more serious complications.

If mild symptoms of *preëclamptic toxemia* develop, the patient is placed on a diet low in fat and proteins, high in carbohydrates and calcium; and **calcium gluconate** or **dicalcium phosphate** and **viosterol** (10 to 20 drops twice daily) are given. **Sunshine baths** are prescribed and **rest in bed** if the symptoms are at all severe.

In severe *preëclamptic* cases, and in cases with *convulsions*, **parathormone** is given in 20 unit doses hypodermically, with **calcium** and **glucose** given simultaneously. **Calcium gluconate** is given by mouth in **glucose lemonade** as soon as the patient is able to swallow.

In 10 cases of *preëclampsia*, 5 mild and 3 severe, and 2 cases of *eclampsia*, this treatment was used by Landry with excellent results.

The physiologists and pharmacologists have long known that any excess of calcium ions slows the heart and that large doses will stop the heart in systole.

In 1931, A. L. Lieberman reported the digitalis-like effect of calcium and cautioned against its intravenous use, as did also W. D. M. Lloyd.

J. O. Bower and H. A. K. Mengle (J. A. M. A. 106: 1151 (Apr. 4) 1936) report 2 cases in which death occurred following the intramuscular injection of digitalis and the intravenous injection of calcium gluconate. They believe that a warning should be issued relative to the *additive* of calcium and digitalis when given simultaneously.

**CAMPHOR.—*Therapeutics.*—**

Camphor has been recommended by D. N. McInturff, Jr. (U. S. Nav. M. Bull. 34:70 (Jan.) 1936) as the ideal method of treatment for *lacerations*, and proves its value in 83 consecutive cases in which there was no primary or secondary infection.

His treatment of lacerated wounds as a result of minor industrial wounds is to flush the wound out thoroughly with **ether** which is allowed to evaporate. This is followed by a **suture** if necessary. The wound is then dressed with sterile gauze saturated with **camphorated oil**. Ether acts as a local anesthetic which assists in the suture as well as being a bactericidal. It is a tissue irritant, but the oil dressing which follows makes this transitory. He also uses it in second-degree *burns* following the application of **amertan** (a tannic acid jelly) the first day; upon the next and subsequent days gauze dressings saturated with **camphorated oil** are employed. Reëpithelization is especially rapid, as there is no secondary infection and no trouble associated with dressing renewal, which is done daily. Treatment may be applied by the patient, who is instructed to remove the outer-dressing, resaturate under-dressing with oil, and re-bind the wound.

**CARBARSONE.—*Poisoning.*—**

Carbarsone caused the death of one patient, as reported by E. Epstein (J. A. M. A.) 106:769 (Mar. 7) 1936).

Chemically, a very close relationship exists between carbarsone, acetarsone and tryparsamide. The reactions to these three drugs are very much alike. The signs and symptoms of tryparsamide toxicity are: dermatitis, jaundice, hepatitis and slight irritation of abnormal kidneys. The following reactions to acetarsone are also reported: malaise, headache, fever, edema, albuminuria,

jaundice, eosinophilia, leukopenia, and exfoliative dermatitis.

Epstein concludes that carbarsone is less toxic in the therapeutic range when given by the therapeutic route of administration than most other related arsenical preparations but is not entirely innocuous.

Care must be taken in administering carbarsone and constant watch must be maintained for signs of intolerance.

**CEVITAMIC ACID.**—With the growing importance of the various vitamins, numerous studies have been carried on with a view to a clear understanding of their chemical structures and physiological action. The various preparations containing vitamin C have been studied in detail. Formerly, cevitic acid was known as ascorbic acid, but more recently it was found that the two were not identical.

Cevitic acid has been used in the treatment of *infantile scurvy*, tablets of 10 mg. ( $\frac{1}{6}$  grain) dissolved in 10 to 20 c.c. ( $2\frac{1}{2}$  to 5 drams) of water being given orally. For intravenous use, the crystalline acid must be used after having been properly neutralized with sodium bicarbonate, as shown by Fisher and Leake. The intravenous approach is valuable particularly in those infants who cannot retain orange juice in any form by mouth. If cevitic acid in solution can be retained orally, a rapid cure may be effected.

**CHOLINE.—ACETYLBETHAMETHYLCHOLINE CHLORIDE.**—*Therapeutics.*—J. T. Gernon, E. E. Ewert and R. D. Herrold (M. Record 141:141 (Feb. 6) 1935) report that the chloride was found to be of value in a series of patients with neuro-pathic disturbances of the bladder, and also in cases which had proved very resistant to treatment.

This drug was used because of its known action on the parasympathetic nerves. Seven patients had the so-called *cord bladder*, 2 associated with sclerosis, 4 with syphilis and 1 with spinal bifida occulta. The drug was given in doses of 200 mgs. (3 grains), well diluted with water, daily for a period of 3 weeks.

*Chronic varicose ulcers*, and *vascular diseases* in which spasm is the major factor, seem to respond exceptionally well to choline therapy, whether administered subcutaneously, orally or by iontophoresis, according to J. Kovacs, L. L. Saylor and I. S. Wright (Am. Heart J. 11:53 (Jan.) 1936). They also found that choline compounds effect only a transient drop in blood-pressure, no consistent change in basal metabolic rate, and very little therapeutic benefit in cases of peripheral vascular disease where organic occlusion is the important factor. They have treated 25 cases of varicose ulcer with only 2 failures. No other treatment was used except plain vaseline during the first few days when necessary. No patients were hospitalized or kept from strenuous duties. The method of treatment employed was a 5 per cent. solution, applied by iontophoresis for 20 to 30 minutes at 20 milliamperes, 2 or 3 times a week. An asbestos cloth saturated in the solution was applied over the foot and leg and as high as the knee, but the electrode was never applied over the affected (ulcerated) area until a firm scab had formed.

E. H. Schwab, W. L. Marr and R. M. Moore (Texas State J. Med. 31:574 (Jan.) 1936) agreed with Kovacs and his associates in the effect on the peripheral vascular disease, but they found also that given intravenously, it is of great use in terminating attacks of *paroxysmal tachycardia* of the supraventricular type. Intravenous injections

produced the following exaggerated symptoms: salivation; lacrimation; warmth and sweating about the head, neck and upper part of the chest; tightness of the chest and sometimes shortness of breath; precordial pain; a momentary increase but subsequent decrease in pulse rate; a transient fall in blood-pressure, some nausea, no vomiting; and active intestinal peristalsis. **Atropine** is a physiological antagonist.

The use of acetylcholine hypodermically in the treatment of *osena* is advocated by Z. Chéridjian and T. Sciclounoff (Presse. méd. 44:1290 (Aug. 12) 1936). Nine cases so treated showed 5 recoveries, 3 improvements, and 1 failure. They believe that the artificial production of hypercalcium might facilitate or reinforce the action of the acetylcholine.

**CINCHOPHEN.—Poisoning.**—W. L. Palmer and P. S. Woodall (J. A. M. A. 107:760 (Sept. 5) 1936) conclude that there is no safe method for the administration of cinchophen.

In the past 20 years there have been recorded 191 cases of cinchophen poisoning including neo-cinchophen. Of these, 88 ended fatally, a mortality rate of 46.3 per cent. The actual incidence of this sequence is undoubtedly much higher than the published reports would indicate. Instances have been cited in which the long-continued use of cinchophen has been without apparent harm until the sudden appearance of jaundice, followed by dramatic death. In some cases the administration of very small doses of the drug under careful observation, with immediate withdrawal on the first evidence of toxicity, has nevertheless proved fatal.

M. W. Comfort (*Ibid.* 107:763 (Sept. 5) 1936) believes that the danger of cinchophen poisoning is so real, that at the Mayo Clinic they consider the

drug should not be used when there is an effective substitute; also surgical procedures should be avoided. They use it only in the treatment of *gout*. He believes the mortality and morbidity can be reduced by its discontinuance on the first manifestations of toxicity, and that the danger of the drug should be impressed on the patient who has recovered from cinchophen poisoning.

**COD-LIVER OIL.**—*Therapeutics.*—Cod-liver oil has been used for the treatment of various conditions, important among them being *infections*. H. Lucke has recommended cod-liver oil ointment for *minor surgery* done by the general practitioner. The ointment is applied locally and the part is bandaged, the latter being changed every 48 hours.

Steel has treated *burns* with cod-liver oil and claims splendid results. He uses lint heavily soaked in cod-liver oil applied to the part and covered with a dressing which is left in place and re-soaked with cod-liver oil every 24 hours, the lint not being removed until after the 48-hour period. Cod-liver oil applied locally hastens recovery and speed with which an indolent area is transformed into one of healthy granulation.

**COPPER.**—*Physiological Action.*—Copper was found to have a very definite influence on the carbohydrate metabolism by H. Schnetz (Ztschr. f. Klin. Med. 121:739 (Apr. 18) 1936). He observed that in normal persons epinephrine hyperglycemia as well as dextrose hyperglycemia could be inhibited by the daily administration of 20 mg. ( $\frac{1}{3}$  grain) of copper. The inhibiting effect of copper in the induced hyperglycemias, as well as the anti-infectious, antianemic and roborating actions of copper, induced the author to try copper medication in several cases of severe *diabetes mellitus*. He found

that with proper therapy the doses of **insulin** could be greatly reduced for the sugar content of the blood and urine decline, and the general condition was greatly improved under the influence of **copper**. The inhibited action of copper seems to influence only the increased sugar content, for the normal sugar content is neither increased nor reduced by copper medication. The author considers that individualization of the dosage is highly important in copper medication and hyperglycemia and that the action of copper is restricted to certain degrees of hyperglycemia. In 2 cases, Schnetz found that insulin therapy could probably not be replaced by the copper treatment.

**DEXTROSE.**—*Therapeutics.*—Method of treating *ozena* and *atrophic rhinitis* by local application of dextrose in chemically pure form is reported by F. Sturm (Arch. f. Ohren-, Nasen- u. Kehlkopfh. 140:207 (Jan. 3) (1936).

For 2 or 3 treatments, the dextrose in powder form was insufflated into the nose; the patient then applied dextro-lanolin salve and occasionally insufflated the dextrose powder. Of 25 cases so treated, 12 were true *ozena*, 7 of a severe type; 11 were cases of *atrophic rhinitis* without fetor; and 2 *rhinitis sicca*. In most cases there was rapid improvement. All the patients with *atrophic rhinitis* were free from symptoms by using 1 or 2 daily applications of the salve. All but one of the cases of *ozena* were definitely improved, and in this case the patient did not employ self-treatment constantly and thoroughly. In all other cases, the crusting and fetor were relieved. In some cases, the associated *pharyngitis* was markedly relieved, although it persisted to some extent. Some patients reported relief of headache, but in no case was there improvement of the sense of smell,

**DINITROPHENOL.—Poisoning.**—The harmful effects of dinitrophenol continue to accumulate as shown in reports in the literature. Two additional cases of granulopenia following the administration of dinitrophenol are recorded by S. W. Imerman and C. P. Imerman (J. A. M. A. 106:1085 (Mar. 28) 1936) which presented several unusual features, *i. e.*, anemia, thrombocytopenia, purpura, and lung abscess. Dinitrophenol is unpredictably toxic in that persons with chronic rheumatism, tuberculosis, alcoholism, renal disorders, and hepatic disease seem to have a lessened resistance.

The rapid development of cataract is another common complication, as investigated by W. W. Boardman (*Ibid.* 105:108 (July 13) 1935) who reported 6 cases. W. D. Horner, R. B. Jones and W. W. Boardman (*Ibid.*) reported 3 cases; 1 case was observed by J. M. Hitch and W. F. Schwartz (*Ibid.* 106:2130 (June 20) 1936).

The Government, through the Chief of the Federal Food and Drug Administration, has issued a warning against the use of dinitrophenol for reducing weight. This drug may produce acute poisoning, the symptoms of which are nausea, gastric and intestinal distress, sweating, flushed skin, high fever, rapid breathing and muscular rigor, followed by death. The drug produces also agranulocytosis and damages the liver, kidneys, heart and sensory nerves. Some of the names under which it has been sold or is now being sold as reported by the Food and Drug Administration are as follows: Nitromet, dinitrolac, nitraphen, dinitrisco, formula 281, dinitrose, nox-ben-ol, re-du, aldinol, dinitrenal, prescription No. 17, slim dinitrole, tabolin, and redusols. (H. E. Hill: J. Indiana M. A. 29:67 (Feb.) 1936).

## ENDOCRINE THERAPY.—

Probably no field of therapeutics has shown more striking advances than the field of endocrine therapy. Various preparations of the different endocrine glands have been made, some of which are satisfactory, with accurate chemical composition determined, while in others the claims are vague and indifferent as far as their chemical structure and therapeutic efficacy are concerned. A standardized **pituitary preparation** was used by Berman in the treatment of *Simmond's disease*. This extract contained the growth hormone, and in a series of 24 patients showing malnutrition, who were sensitive to insulin and had a low blood sugar and blood nitrogen, there was an average weight gain of approximately 32 pounds in 3 to 6 months, with a corresponding improvement in general fatigability and asthenic state.

The anterior **pituitary-like hormone** was used by Browne for treating 37 cases of *functional dysmenorrhea*. The dosage was 0.5 c.c. (8 minims) daily for 5 days. Treatment was more effective when begun about 2 weeks before the expected time of menstruation. Browne states that the results have been most promising.

Novak has called attention to the error of feeding *ovarian tablets* by mouth for ovarian underfunction. He states that nearly all of the older preparations are entirely or almost entirely inert. To produce menstruation in the human females, 2 ovarian hormones are necessary, (1) that of the follicle and (2) that of the corpus luteum. They must be properly balanced in a quantitative way and must operate in a certain sequence to bring about changes in the uterus to produce menstruation. Ovarian therapy is merely a substitution therapy but in no way increases the ovarian function, and, moreover, evi-

dence suggests that extensive or prolonged estrin therapy actually inhibits the activity of the anterior hypophysis on which gland depends the efficacy of the menstrual cycle.

**EPHEDRINE.**—*Untoward Effects.*—A peculiar side reaction from the use of ephedrine was observed by J. J. Valentine and J. S. Fitzgerald (J. Urol. 34:314 (Oct.) 1935), *viz.*, acute retention of urine. They report 3 cases in which an attempt was made to use it in the treatment of dribbling or weak sphincteric control. From these observations, they believe that the retention occurs only in those patients who are developing prostatism, or are reaching the prostatic age. Red blood cells and albuminuria were present in all three cases and cleared on cessation of the drug.

They conclude that ephedrine causes retention by producing a spasm of the internal sphincter which is greater than the voluntary control.

**EPINEPHRINE.**—*Physiological Action.*—The spasm of the cervix which occasionally results following the injection of pituitary extract in the second stage of labor before the delivery of the placenta is believed by G. G. Copeland (Canad. M. A. J. 34:317 (Mar.) 1936) to be due to an idiosyncrasy. By the use of 5 mm. of epinephrine solution 1:1000 in one case, the spasm began to relax in 3 minutes and in 5 minutes the cervix opened to the size of a fist and was soft in consistency. Manual expression of the placenta was easily accomplished.

**ERGOT.**—*Preparations.*—The new oxytocic principle of ergot has been named *ergonovine* by the Council of Pharmacy and Chemistry, to replace the various terms used amongst investi-

gators, *i. e.*, ergotamine (Dudley and Moore), ergotocin (Kharasch and Legault), ergobasine (Stoll and Burckhardt), and ergostetrine (Thompson).

Ergonovine comes under the broad definition of an alkaloid. It differs chemically from the previously isolated alkaloids of ergot, in that it is not precipitated by Meyers' reagent in a dilution higher than 1:6000, while the other alkaloids are precipitated by that reagent in dilutions as high as 1:2,000,000.

It is a colorless, crystalline material appreciably soluble in water, imparting to the latter a weak alkaline reaction. It may be crystallized in long, fine, needle-shaped forms from such solvents as chloroform, benzene and trichloroethylene.

The empirical formula is  $C_{19}H_{23}N_3O_2$ . Prolonged heating at a higher temperature inactivates the material.

The degradation of ergonovine has yielded lysergic acid, a basic hydrogen product as propanolamine.

Ergonovine is a rather unstable substance at high temperatures. At ordinary temperatures, the solution of the salts is relatively stable. It is assayed by the U. S. P. cock's comb method and by the isolated uterine response. It has a stimulative reaction on the sympathetics.

Ergonovine is effective by oral administration in small doses. When administered in doses of from 0.2 to 0.4 mg. ( $\frac{1}{300}$  to  $\frac{1}{150}$  grain) by mouth, it causes a typical ergot response in 6 or 8 minutes. The uterus develops tonicity and following the initial tetany, which lasts 5 or 6 minutes, uterine motility is established, which becomes more vigorous in character as the uterine tone diminishes. Good uterine motility continues for at least 2 hours, so that frequent administration of the drug is not necessary. Intravenous ad-

ministration in doses of 0.2 mg. ( $\frac{1}{300}$  grain) produces an immediate response, particularly marked by the high degree of tone, which is of great importance in its therapeutic application.

The drug does not affect the pulse, blood-pressure or urinary output. Its toxicity is extremely low and its cumulative action is likewise negligible, since prolonged administration in patients resulted in no signs of toxicity. Oral tablets can be kept indefinitely. The aqueous solution is as yet not sufficiently stable. The powder, therefore, is best dissolved in water just before it is to be administered intravenously.

M. E. Davis, F. L. Adair and S. Pearl (J. A. M. A. 107:261 (July 25) 1936) observed the action of ergonovine in some 200 *labors* completed by postpartum hemorrhage with spectacular results. The uterus contracted firmly and remained so following the intravenous administration of 0.2 mg. ( $\frac{1}{300}$  grain) of ergonovine. They believe that the use of oxytocic drugs in the puerperium is of value in aiding involution, increasing uterine tone and motility. The uterine activity results in complete evacuation of the uterine cavity of its lochial secretions, a more rapid decrease in the size of the uterus and some limitation of the spread of infection if present. They gave ergonovine maleate from 0.2 to 0.4 mg. ( $\frac{1}{300}$  to  $\frac{1}{150}$  grain) 3 times daily in cases presenting a postpartum hemorrhage, a difficult forceps, intrauterine manipulation, abnormal lochia, fever regardless of the cause, or delayed involution without cause. This therapy is continued for at least 3 days or as long as is necessary. If uterine contractions become too painful, the dose of ergonovine maleate is reduced or the drug omitted.

The newly-recognized oxytocic principle of ergot has many advantages, according to J. L. Tuck (Am. J. Obst.

and Gynec. 30:718 (Nov.) 1935), who found that the lochia is almost free from a bloody tinge after 3 or 4 days when the alkaloid has been used in the early *puerperium*. The theretical objection raised by many who have no practical experience is the danger of infection in the genital tract by the rectal administration of the oxytocic. Among 240 patients receiving the drug orally, and hypodermically, the morbidity was 14 per cent. In 128 patients receiving the drug rectally, at delivery, the morbidity was 9 per cent. (morbidity consisted of elevation of temperature of more than 100° F.). He concludes that the rectal route, when used properly, offers no more danger of infection in the mother than the oral and hypodermic routes. The results in 332 women were uniformly satisfying. Rectal administration is recommended, as the contractile response of the uterus is more rapid by from 1 to 2½ minutes.

### ERGOTAMINE TARTRATE.

—*Untoward Effects.*—Attention is called by W. M. Yater and J. A. Cahill (J. A. M. A. 106:1625 (May 9) 1936) to the serious toxic disturbances resulting from overdosage, first among which is *gangrene* of the extremities. The cause of the gangrene is occlusion of the medium sized and small arteries and arterioles by severe constriction and thrombosis. He advises against the use of the drug in cases of febrile puerperium, and in cases of severe toxemia from any cause, or in patients who have presented evidence of vascular disease, functional or organic.

At the present time, the use of the drug should probably be limited by the profession at large to appropriate obstetric and gynecologic conditions and to the relief of migraine. Toxic results are less liable to follow the oral administration than the injection method. Care-

ful watch should be maintained for the appearance of any toxic symptoms, including signs of impaired circulation of the extremities.

S. E. Gould, A. E. Price and H. I. Ginsberg (*Ibid.* 106:1631 (May 9) 1936) report a case of *gangrene* of both lower extremities followed by death after the injection of ergotamine tartrate.

**Therapeutics.**—The reported use of ergotamine tartrate for the relief of *migraine headache* has appeared since 1926 in the French and German literature. Reports continue to accumulate, all of which give a high percentage of success. The treatment, however, remains empirical. It may be an effective means of aborting a headache but it is not to be considered a cure for migraine. A number of migrainous types of headache are not relieved by it.

Lennox and von Storch used ergotamine tartrate in 120 cases of *chronic migraine* and found that the initial use of the drug gave prompt and complete relief from headache in 107 of the patients, or 89 per cent. When given by injection, relief was obtained in 90 per cent. in 15 to 30 minutes; when given by mouth, 82 per cent. obtained relief in 45 to 90 minutes. The drug is contraindicated in arterial disease, because ergotamine tartrate raises the blood-pressure. Excessive and long-continued use carries the danger of ergotism. When *nausea and vomiting* occur, **atropine sulphate**,  $\frac{1}{130}$  grain (0.5 mg.) should be given.

F. L. McNaughton (Canad. M. A. J. 33:664 (Dec.) 1935) advises the use of 0.5 mg. (1 c.c. ampoule) given subcutaneously or intramuscularly at the onset of an attack and repeated if necessary. Half of this dose is advised at the trial, as 0.25 mg. may be sufficient in some cases. Relief is felt in from 35 to 90 minutes following subcutaneous injection. Daily use to prevent recur-

rence of an attack is not advised. Unpleasant symptoms are nausea, vomiting, muscle pains, and substernal sensation.

W. G. Lennox, T. J. C. von Storch and P. Solomon (Am. J. M. Sc. 192:57 (July) 1936), who in 1935, reported 90 per cent. favorable results in treating 120 cases suffering from severe *periodic headaches*, administered the drug in the same manner to 46 persons who had nonmigrainous headaches. The headaches of 15 of these 46 patients were relieved, 63 per cent. were unchanged and 22 per cent. became worse.

The use of ergotamine tartrate in the treatment of 97 patients and 1042 episodes in 89 cases were completely checked by M. E. O'Sullivan (J. A. M. A. 107:1208 (Oct. 10) 1936). It was found that the earlier the medication was given, the better was the result. Its subcutaneous use will never fail to check an attack in a patient previously relieved if the dose is adequate. The minimum effective dose is directly proportional to the severity of the attack and when the patient anticipates a bad attack of *migraine*, a slightly larger dose should be given. A much larger dose is required orally at times, 4 to 5 mg. ( $\frac{1}{16}$  to  $\frac{1}{12}$  grain). Relief of the attack is usually obtained in from 1 to 8 hours. *Untoward effects* of the drug may be relieved by the simultaneous administration of  $\frac{1}{100}$  grain (0.65 mg.) of **atropine** or **calcium gluconate** intravenously.

S. S. Lichtman (*Ibid.* 107:148 (July 11) 1936) gives the following outline of dosage in cases for the relief of *pruritus* in jaundice and uremia. The first dose of 1 mg. ( $\frac{1}{65}$  grain) is given orally at night. If it is beneficial, the patient sleeps undisturbed by itching. Three doses are then given by mouth the following day. The drug is discontinued if no relief is obtained and if pains and paresthesias appear in the limbs. If partial relief is obtained, the drug is



continued for 3 more doses. Single doses may produce remarkable results. When ineffective, even larger and repeated doses may fail to produce the desired therapeutic response. Standing orders should not be issued, but the dose given once or twice and continued only with strict supervision by the physician of the effects of the drug on the patient.

**ETHYLENE GLYCOL.—Administration.**—Ethylene glycol-magnesium sulphate paste has been found by J. W. Hinton (Arch. Surg. 33:210 (Aug.) 1936) to act more rapidly than magnesium sulphate or other ointments. It is more successful in arresting or localizing infections than other methods of treatment. It is made by mixing magnesium sulphate, 60 per cent., and ethylene glycol, 40 per cent., by volume. The ethylene glycol is brought to a boil and the magnesium sulphate slowly added to the glycol preparation and thoroughly stirred until the solution becomes adherent to the stirring rod. It is then transferred to an electrical mixer and kept in constant motion for from 20 to 25 minutes. The paste is then allowed to stand for 10 days before it is used. The preparation should be stirred daily for 5 minutes during this period. It is usually changed every 8 hours when treating severe cellulitis.

The object in using this preparation is to have a medicament with hypertonic properties so that continuous osmosis will take place in the inflammatory area and by this means the infection will be localized and the edema relieved. The preparation has been used for 2 years in more than 100 *inflammatory conditions* from a simple *furuncle* to a severe *cellulitis*, with astounding results.

**GOLD.—Therapeutics.**—Gold and sodium thiosulphate were used in 76 cases of *lupus erythematosus* by C. S.

Wright (Arch. Dermat. and Syph. 33: 413 (Mar.) 1936) over a period of 10 years. Twenty-eight cases were regarded as cured, 26 were almost cured or greatly improved, 13 were improved moderately, and 9 failed to respond favorably to the treatment. The amount of gold and sodium thiosulphate required for cure varied from a minimum of 12 mg. (2 grains) in one patient to a maximum of 2,750 mg. (40 grains) in another. Thirteen of the patients suffered a relapse of one type or another from the gold, the commonest of which was a scarlatiniform dermatitis which occurred in 8 cases. The warning signs of intolerance should be watched for in order to prevent fatalities. All reports are in agreement on the *toxicity* of gold compounds. Nephritis with albuminuria, edema and sometimes raised blood urea may occur. Shock and collapse occurring immediately after an injection has been reported. Pyrexia has been noted more often by some observers than by others and is probably more frequent when an intravenous preparation is used. Stomatitis and diarrhea sometimes occur. S. J. Hartfall and H. G. Garland (Lancet 2:8 (July 6) 1935) report toxic reactions in 45 of their 100 cases. The most generalized pruritus occurred in 36 cases; erythema developed in 28 of these, and 4 went on to desquamation. Diarrhea developed in 10 cases. Soreness of the mouth was complained of in 9 cases and 3 went on to ulceration. In 4 cases vomiting occurred within a few hours of the injection and in 1 patient there was immediate nausea without vomiting. Isolated cases of hyperkeratosis of the soles, pustular dermatitis of the hands and feet, labial edema, herpes zoster, erythema nodosum, lichen planus and purpura were noted. Three of their patients died.

There is a considerable amount of work indicating the therapeutic effectiveness of

gold salts in *rheumatoid arthritis*. The best preparation, mode of administration and dosage are not a matter of general agreement. The toxicity is marked. It seems that aurotherapy is promising in a restricted field when some of the doubtful factors become clear and the necessary precautions against toxic reactions standardized. At the present time no one who is not thoroughly familiar with the indications and dangers should attempt its use. (Editorial. J. A. M. A. 105:2163 (Dec. 28) 1935).

*Harmful results* following gold therapy were reported by P. Ellman and J. S. Lawrence (Brit. M. J. 2:622 (Oct. 5) 1935), who present a fatal case of hemorrhagic purpura with agranulocytosis.

E. Bernard and M. Morin (J. A. M. A. 107:49 (July 4) 1936) report a case of neurological disturbances, stomatitis and psychic disturbances. Charles Flandin and his associates (*Ibid.*) report 2 cases of severe stomatitis.

**HISTAMINE.—Therapeutics.**—Weissenbach and Perles (J. A. M. A. 107:803 (Sept. 5) 1936) report on the use of histamine in the treatment of *chronic rheumatism*. If the histamine is injected intradermically instead of into the muscles, the pain of the latter method can be avoided. A solution containing 0.5 mg. ( $\frac{1}{12}$  grain) of histamine hydrochloride per c.c. is used for each sitting, the average dose injected being from 0.25 to 0.5 mg. ( $\frac{1}{25}$  to  $\frac{1}{12}$  grain), to which a local anesthetic (phenylpropionate of para-amino-benzoylamine-ethanol) in the proportion of 0.5 mg. ( $\frac{1}{12}$  grain) to the same amount of histamine is added.

A special 1 c.c. syringe graduated in 0.05 cm. and a very fine needle such as is used for intradermal reactions is essential for injection into the dermis of the region as close as possible to the seat of pain. A series of 2 to 10 injections

is given every day or every second day, according to the results obtained. The relief of pain is almost immediate and may be permanent after the first injection, but it may recur after an interval of from 6 to 18 hours. Repetition of the injections appears to have a cumulative effect. The muscular contracture and functional disability disappear in direct proportion to that of the cessation of the pain.

In 41 patients suffering from all types of acute rheumatism, but especially of the chronic form, the treatment has been successful after the first injection in 85 per cent. of the cases. At times, painful contractures of several months' and even years' duration disappeared after 2 or 3 treatments, often after a single treatment.

**HISTIDINE.—Therapeutics.**—**PEPTIC ULCER.**—The use of histidine in the treatment of *peptic ulcer* is reported on by D. J. Sandweiss (J. A. M. A. 106:1452 (Apr. 25) 1936). He treated 67 patients, some with diet-alkali regime and others with histidine. Of the patients treated with diet-alkali, 51 per cent. became symptom-free and 20.7 per cent. were moderately improved (a total of 71.7 per cent. of favorable responses).

Of 17 patients treated with histidine after the diet-alkali management failed to produce remissions, 52.9 per cent. became symptom-free and 17.6 per cent. moderately improved (a total of 70.6 per cent. of favorable responses).

Of 9 patients treated with the diet-alkali after histidine failed to produce remissions, 42.8 per cent. became symptom-free and 28.6 per cent. moderately improved (a total of 71.4 per cent. favorable responses).

By changing from one treatment to another and trying all means at hand to "tire out the ulcer," 73.5 per cent. became symptom-free and 13.4 per cent.

moderately improved, a total of 86.5 per cent. of favorable responses. Of the 9 patients not responding to medical management, 4 had ulcer complications necessitating surgery and 5 had medical complications such as myocarditis, hyperthyroidism or arteriosclerosis.

Eighty-five per cent. of the patients treated with histidine, developed recurrences of the ulcer symptoms within 6 months after treatment. Only 31 per cent. with ulcer symptoms returned at the end of 6 months.

If 5 or 6 (at the most, 8) consecutive daily histidine injections do not cause complete disappearance of all ulcer discomforts, the hope of producing a remission or of prolonging a symptom-free interval by further histidine injections is negligible.

Of 24 patients checked by 8 x-ray examinations after histidine treatment, not one showed disappearance of the ulcer.

Sandweiss believes that the results obtained do not warrant routine injections of histidine in all ulcer patients, but that it is "extra artillery" in patients not responding to the diet-alkali-antispasmodic management.

A report was prepared by K. A. Martin (*Ibid.* 106:1468 (Apr. 25) 1936) for the Council of Pharmacy and Chemistry of the American Medical Association after a comparison of 41 selected patients with acute symptoms and radiological signs of active peptic ulcer who were treated with histidine hydrochloride. A crater was demonstrated radiographically in 30 of the 41 patients. The immediate response to this therapy was fairly uniform and prompt, 30 patients being relieved of their symptoms at or before the conclusion of the treatment. Fourteen of the group showed radiological evidence of a healed ulcer, whereas 12 showed a crater still present. Eleven showed no

improvement symptomatically or radiographically.

The period of observation varied from 6 months to 1 year; 32 patients have been under observation for 10 months. Thirteen are still symptom-free and 26 have had one or more relapses. Of the 12 who still showed a crater, only 3 have remained symptom-free, but of 14 where no crater could be demonstrated after treatment, 10 have remained asymptomatic.

A similar series of 40 patients were treated with the usual ambulatory diet-alkali ulcer regimes. At the end of the first 4 weeks of treatment, 31 were symptom-free. The period of observation varied from 10 months to 1 year. Sixteen have remained symptom-free, whereas, 24 had one or more relapses. The symptomatic and radiological response in the histidine series was not quite as good as that in the diet-alkali regime series in either the initial or sustained effects. Symptomatic relief with persistent crater is almost equally common to the two groups, as is a relapse of symptoms. The clinical improvement succeeding histidine hydrochloride therapy in acute peptic ulcer appears to be symptomatic and transient.

Chronicity and rhythmicity are characteristic features of the peptic ulcer. Histidine appears to have no effect other than to alter the rhythm slightly. It showed no effect on the hydrochloric acid secretion in their series. In the quantity used, it appeared to be harmless.

D. Smith (Brit. M. J. 2:154 (July 27) 1935) reports favorably on the use of histidine hydrochloride in a series of 12 cases in which in a fair percentage the ulcers could no longer be seen radiologically after the course of treatments. He does not acclaim it as a certain cure for peptic ulcer, even of the simple lesser curvature type, but feels that the results reported definitely prove it to be of value

in hastening the healing of such ulcers and justify further trial and study as to the nature of its action.

J. T. Eads (*Am. J. Digest., Dis. and Nutrition* 2:426 (Sept.) 1935) reports 35 cases treated with daily doses of histidine given intramuscularly with the following results: 6 cases cured clinically and radiologically; 9, amelioration of symptoms, x-ray findings unchanged; 8, clinical improvement; 12, unimproved; 3 cases later showed improvement when placed on a strict ulcer regime, although the regime had no previous effect.

In a series of 73 cases, I. F. Volini and R. F. McLaughlin (*Illinois. M. J.* 69: 39 (Jan.) 1936) submitted the following results: Immediate results were satisfactory in all except 11 cases. Six months after the treatment 4 of the patients had recurrences of the symptoms. Fifty-eight were free from symptoms. Twenty-seven of these showed complete disappearance of the x-ray signs of ulcer, while 10 showed improvement in the radiological signs and 21 showed no change. The x-ray evidence of healing was more pronounced in the marginal and in the gastric ulcer cases than in the duodenal cases.

**INSULIN.—*Therapeutics.***—The treatment of *diabetes* with high carbohydrate diets and insulin is discussed by Joslin. The effectiveness of insulin increases as the carbohydrate is increased and the fat in the diet is decreased, as judged by the ratio of units of insulin to grams of carbohydrate utilized. The use of such diets overcomes hypercholesteremia. In the majority of patients, the levels of the blood sugar are reduced after the administration of high carbohydrate diets and it is said that hyperinsulinism is less apt to develop.

Insulin was employed by M. P. Chen, Y. L. Ch'eng and R. S. Lyman (*J. Nerv. and Ment. Dis.* 83: 281 (Mar.)

1936) as a substitute for morphine and other *drug addiction*. The method used was complete withdrawal of the drug for which insulin in high doses, was substituted with food and luminal as soon as the withdrawal symptoms appeared. The insulin was given in doses of 20 to 30 units every 3 hours. This high dosage of insulin was kept up for 3 to 5 days. The insulin causes an intense craving for food and the patient is allowed to eat all that he desires. When food is thus freely permitted, a marked hypoglycemia does not develop; the lowest blood sugar found in the cases treated was 78 mg. Muscular spasms and twitching developed in a few cases, but these symptoms and many others suggesting hypoglycemia were promptly relieved by giving glucose or orange juice. In the more successful cases there is only a short period of irritative symptoms and then, following the taking of more food, there is a period of relaxation and gain of weight.

The use of insulin in treating *dysmenorrhea* is suggested by A. Altschul (*J. A. M. A.* 106:1380 (Apr. 18) 1936). He found in a group of 12 cases, all nulliparous, suffering from primary or essential dysmenorrhea, that 10 received practically total relief from menstrual pain by using insulin from 3 to 7 days before or during the period. Two patients were only partially relieved. Dosage varied from 7 to 15 units.

**PROTAMINE INSULINATE.—*Therapeutics.***—In treating diabetes, with insulin, the regulated continuous secretion from the normal pancreas into the portal vein is replaced by a few daily injections into the subcutaneous tissue. Serious disturbance is avoided only because the organism has other methods of regulating the blood sugar than to vary the rate of insulin secretion.

H. C. Hagedorn, B. Norman Jensen, N. B. Krarup and I. Woodstrup (*J. A.*

M. A. 106:177 (Jan. 18) 1936) have been working in the Institute of Steno Memorial Hospital on a method to retard the rate of absorption to prevent the pronounced oscillations of the blood sugar and as a result introduced protamine insulinate.

Protamine is an amorphous basic substance rich in nitrogen, found in the spermatid fluid of salmon. On decomposition, it yields arginine, lysin and histidine. The protamine insulinate solution is adjusted to the pH of body fluids, whereby the protamine insulinate is precipitated. Injected protamine insulinate being relatively insoluble, tends to be absorbed slowly and over a relatively longer period of time than ordinary insulinate, and due to its breaking down at a slower rate, the blood sugar lowering effect is increased considerably.

H. F. Root, P. White, A. Marble and E. Stotz (*Ibid.* 106:180 (Jan. 18) 1936), using Danish leio insulin of 40 units strength, added to a given vial 1 c.c. of a solution containing protamine and sodium phosphate. The vial is shaken before each injection of insulin. They used the drug in 15 patients who have been troubled to a greater or less degree with severe insulin reactions and have in general, confirmed the work of Hagedorn and his associates. This new preparation is still in the experimental stage and further work is necessary, both in insulin laboratories and in diabetic clinics, to determine when and how and in which patients protamine insulinate or some related product can best be used. It does not supplant ordinary insulin, as the two usually must be used in the same patient at different times of the day, and is of no special value in those cases now adequately treated with insulin.

One patient observed by F. M. Allen (*Ibid.* 107:430 (Aug. 8) 1936), who had been particularly difficult to control

with insulin was treated with protamine insulinate. Preliminary studies of the blood sugar were made under direct observation and showed satisfactory delayed reduction with the protamine insulinate. A prolonged attempt was made to find any quantities or timing of doses that would control the sugar with 1, 2 or 3 daily injections alone. This was unsuccessful. Combinations of old and new insulin doses were tried at various hours. The finding of a satisfactory combination seemed impossible and the use of protamine insulinate in this case had to be abandoned. Instead of a greater potency, there was found an inability to control the sugar more than with the former dose of insulin. Instead of smoother blood curves, the fluctuations of hypoglycemia and hyperglycemia were more violent than with the old insulin. Allen believes the present form of protamine insulinate is most fully adapted to the more moderate grades of diabetes. It has not settled the problem of the control of sugar in the most severe and difficult cases, in which the old insulin must be used either partially or wholly.

The great fluctuations of blood sugar with the old insulin could mostly be prevented by proper timing and other simple devices. Likewise, the best results will probably be obtained with the new insulin by adaptation to meet individual needs.

*Crystalline insulin* was studied by H. A. Freund and S. Adler (*Ibid.* 107:573 (Aug. 22) 1936) in a series of controlled experiments and they found that this compound had a similar action to protamine insulin. It diminishes the fluctuations in the blood sugar levels and also decreases the severity and frequency of the hypoglycemia reactions commonly seen with the use of the standard insulin. Crystalline insulin is more rapid in onset of action and shorter in the

duration of its effect on the blood sugar level in contrast with the protamine insulin. Its action on the blood sugar level lasts for a period of from 9 to 8 hours and returns slowly to its normal level. It is similar to standard insulin in that it is a stable compound and is dispensed in a single solution.

Similar results were obtained by M. P. Mains and C. J. McMullen (*Ibid.* 107:959 (Sept. 19) 1936) in a series of 22 cases at the Cook County Hospital. Their supply was kept at room temperature for 4 months with no decrease of potency. Over a period of 4 months, no untoward reaction either local or general was noted following the injection of the product, nor was any increase of discomfort noted over that from regular insulin.

#### IODINE.—*Untoward Effects.*—

Potassium iodide is often automatically used in the treatment of *lead poisoning*. K. Fellingner (*Med. Klin.* 32:600 (May) 1936) observed a number of patients so treated in whom symptoms, more or less severe, of *hyperthyroidism* developed. Symptoms such as profuse sweating, emaciation, nervousness, and mild tremor were ascribed by the patients and also by their physicians to the lead poisoning. However, as the symptoms were observed only in the cases of lead poisoning in which iodine therapy had been used, and since in the early cases they had a tendency to disappear after the medication was discontinued, it cannot be doubted that the symptoms were caused by the iodine.

Younger patients are more apt to develop iodine hyperthyroidism but it is occasionally observed in older individuals. Potassium iodide, he believes, is best for the after treatment of lead poisoning in the so-called state of latency, since it aids in the mobilization and elimination of the lead deposits in the organism,

whereas in the earlier stages, it may even elicit colic, as it is now generally accepted that the lead which circulates in the blood and not the lead which is deposited in the body causes the symptoms. It is essential to keep the patient under strict supervision so long as he receives iodine therapy and as soon as tachycardia, sweating or emaciation develop, it should be broken off.

**IRON.—*Therapeutics.***—Time tested therapeutic methods are often forgotten as a result of modern scientific research. Iron salts have been used to a great extent intravenously in the management of *secondary anemias*.

G. H. Whipple and F. S. Robscheit-Robbins (*Am. J. M. Sc.* 191:11 (Jan.) 1936; and P. F. Hahn and G. H. Whipple (*Ibid.* 191:24 (Jan.) 1936), in a series of experiments kept dogs anemic by repeated blood letting and measured the hemoglobin regenerating power of iron salts. They found that colloidal iron given intravenously induces quantitative new hemoglobin formation in the ratio of 3 mg. of iron to 1 gram of hemoglobin. Iron by mouth will produce an increase of hemoglobin contents of dogs' blood at a slower rate than when given parenterally. They found that ferric, ferrous, and reduced iron all are equally effective in relieving the anemia. Food iron is no more effective than simple metallic iron. The important factor was found to be not the kind of iron given, but the relative amount of the metal itself.

With depletion of the iron reserves and on a diet poor in iron, there is no difficulty in maintaining the anemia. The iron stored in muscles is not lost during such emergency nor is its amount increased by iron feeding. Muscle iron, they believe, is of importance for the maintenance of the power of motion and that the animal might even die of par-

alysis if the functional ability of the heart were impaired by the loss of its iron content. Colloidal iron injected intravenously in iron depleted animals is returned as iron hemoglobin. With liver feeding the amount of hemoglobin formation is increased in an amount greater than can be expected from its iron content alone. Castle found that the optional dose of iron by mouth for the production of new hemoglobin in anemic adults was 1 Gm. (15 grains) of metallic iron per day. Such a dose of the drug should result in new hemoglobin formation at the rate of 1 per cent. a day. Iron therapy should be continued for a long period in order to obtain satisfactory clinical results. The content of metallic iron in the preparation used must be borne in mind and enough of it prescribed to equal approximately 1.5 Gm. (23 grains) of metallic iron daily.

**LIVER THERAPY.**—Since the discovery by Whipple that liver is effective in the treatment of anemia, a great deal of work has been done in this field. There is no substitute for liver in the treatment of primary anemia. The technic of administration has been under consideration for some time.

Vaughan has used liver in combination with iron. As a matter of fact, liver in any form is effective. By mouth it may be administered only for short periods, due to the difficulties of administration; the intramuscular route is probably superior. For patients in relapse, one dose of intramuscular extract daily for 3 successive days, followed by a weekly injection until the remission is complete, is described and recommended by Wilkins.

#### **MAGNESIUM SULPHATE.**—

**Therapeutics.**—Magnesium sulphate, hypodermically, was employed in *whooping cough*, *asthmatic bronchitis*, and

*spasmodic cough* of unknown etiology, with or without vomiting, in the treatment of 60 children by A. V. Freyere (*Semana méd.* 43: 537 (Aug. 20) 1936). One to two c.c. (16 to 32 minims) of a 15 per cent. solution was used daily every second or third day, according to the seriousness of the disease. In all the patients so treated (except two suffering from asthmatic bronchitis) the treatment produced antispasmodic and sedative effects which lasted for 5 or 6 days. The asthmatic cries and the whooping cough paroxysms and vomiting were controlled generally from the first injection. No patient showed signs of local or general intolerance and no complications set in. *Contraindications* are: cystitis, nephritis and meningitis. *Respiratory paralysis* would be the result of an overdose of magnesium sulphate and would require an immediate intravenous injection of calcium chloride or a subcutaneous injection of atropine.

**MANDELIC ACID.**—**Therapeutics.**—The results of treatment of *urinary infections* with mandelic acid, as advocated by Rosenheim, are reported by D. M. Lyon and D. M. Dunlop (*Brit. M. J.* 2:1096 (Dec. 7) 1935). They used the sodium salt in a neutral mixture and ammonium chloride in doses sufficient to give a pH below 5.5.

Out of 16 cases (10 of chronic types), the urine was rendered sterile in all but three cases; relapses occurred in 4 cases after treatment was discontinued, but in 3 of these the relapse was successfully treated with mandelic acid. The authors advise that treatment should not be discontinued immediately after the urine has become sterile.

H. E. Holling and R. Platt (*Lancet* 1:769 (Apr. 4) 1936) used sodium mandelate, 50 grains (3.2 Gm.); syrup of orange, 1 dram (4 c.c.); and enough

water to make 1 ounce (30 c.c.), given in water 4 times a day, preceded by a solution of ammonium chloride, 30 grains (2 Gm.) and 15 minims (1 c.c.) of liquid extract of licorice in enough water to make 1 ounce (30 c.c.). Water intake was limited to 2 pints (1000 c.c.) unless great thirst was complained of. The urine must attain a pH of 5.3 or less. In every uncomplicated case of *acute or chronic pyelonephritis*, the urine was rendered sterile by mandelic acid in 2 to 21 days. To obviate the unpleasantness of two such mixtures, the authors found that 34 grains (2.2 Gm.) of ammonium mandelate, 4 times daily, produced a satisfactory urinary acidity, and that ammonium mandelate is a convenient means of administering mandelic acid. Thus in the majority of cases, the use of ammonium chloride can be obviated. The dose of ammonium mandelate is probably the same as that of the sodium salt.

**MERCURY.—Poisoning.**—With bichloride of mercury poisoning, it must be kept in mind that only about one-half of the patients who take bichloride develop symptoms of mercury poisoning, according to E. Hull and L. A. Monte (New Orleans M. and S. J. 88:455 (Jan.) 1936). It is difficult to explain why certain persons who take bichloride develop no symptoms at all, while in others rapid fatal intoxication is produced. Most of the cases of bichloride poisoning follow ingesting while occasionally it follows the use of bichloride douches or the insertion of a tablet into the vagina. Rarely, symptoms have developed as the result of a bichloride bath or an enema containing the drug. Bichloride is much more toxic when administered by vagina than when taken by mouth, symptoms having been known to develop as early as an hour after the insertion of a tablet into the vagina.

*Prognosis.*—Half of the individuals who take bichloride develop mercury poisoning and about half of these die. A study of the case records of about 400 cases and observations of 150 cases by the authors, bring out the following points in the prognosis:

1. It is very good if less than two tablets have been taken by mouth.
2. Patients rarely succumb who have taken one tablet or less.
3. Prognosis is more favorable if taken undissolved than if taken in a solution.
4. It is more favorable if taken shortly after a meal than on an empty stomach.
5. Early appearance of toxic signs give a poor prognosis. On the other hand, if no signs of poisoning appear for 48 hours after the poison has been taken, the out-look is very favorable.
6. Patients rarely recover from severe shock, and the prognosis is also unfavorable if significant diminution in urinary output persists for more than 2 or 3 days, particularly anuria lasting 24 hours.
7. If a total nonprotein nitrogen exceeds 200 mg. per cent. or the creatinine 5 mg., the outlook is almost hopeless. Eighty-five per cent. of the patients die with severe intoxications and in nearly all of these the intoxication is markedly severe within 2 days after the poison has been taken.

*Treatment.*—In the treatment, the administration of **milk** or **egg white** as an emergency measure before the physician arrives is to be recommended. Hull and Monte believe that the sulphur compounds are of little value and are at present continuing the use of **sodium formaldehyde sulfoxylate**. It too, is probably not of any value, and they believe that it should not supplant prompt and thorough **gastric lavage**.



The following outline of *treatment* has been used for the past 4 years by Hull and Monte:

1. Thorough **gastric lavage**.
2. Measures to combat shock, if it is present. The use of **morphine**, the intravenous administration of **glucose** and **saline**, and the use of **external heat** is indicated. If shock does not respond to these measures, **acacia solution** is given intravenously, or **transfusions of citrated blood** are given. If the patient is in shock when first seen, it is important to delay lavage until measures have been taken to combat shock, for a patient in severe shock may die during an attempt at lavage.

3. The early administration of large volumes of **fluid**, together with **glucose** and **salt**, by parenteral routes, in order to combat dehydration, acidosis, and chloride depletion. During the first two days of the intoxication, about 5000 c.c. (5 quarts) of fluid are given daily. The **intravenous drip** is the most convenient method of supplying fluid.

4. Careful observation of the patient (which includes daily estimations of the total N. P. N. of the blood, blood chloride, and plasma carbondioxide combining power), and the treatment of symptoms and obvious physiologic disturbances as they arise. *Vomiting* is treated by gentle **gastric lavage** and the use of **sedatives**, *diarrhea* by the use of **irrigations of normal saline solution** and the occasional use of **mildly astringent enemata** (such as 1 per cent. **tannic acid**); *abdominal distention* by the same methods used by the surgeon in the treatment of adynamic ileus. Should the blood chloride remain below normal, 2 per cent. saline is substituted for normal saline; if the plasma CO<sub>2</sub> combining power falls below 40 volumes per cent. **sodium bicarbonate** is given intravenously. In the writers' experience, 500 c.c. (1 pint) of 5 per cent. bicar-

bonate solution raises the CO<sub>2</sub> combining power about 8 volumes per cent. in most patients. **Transfusions** are given if *profuse hemorrhage from the bowel* occurs.

The greatest single problem is the decision as to how much fluid to give patients who are secreting very little urine or none at all. At present, the writers feel that in the absence of edema, about 3000 c.c. (3 quarts) of fluid should be given daily above the amount lost in the stools and vomitus (approximately the amount required by a normal person), and that salt should be given with the fluid if the blood chloride is below normal. If any edema at all appears, the amount of fluid is reduced to about 1800 c.c. (1½ quarts) daily (the amount lost through the skin and lungs in a normal person) and the use of salt is discontinued. In the presence of vomiting and tympanites all of the fluid is given by parenteral routes; if the abdomen is flat and no nausea is present, most of the fluid is given by mouth.

Between July, 1932, and April, 1934, 33 patients who had taken bichloride of mercury were treated by this method. There were 4 deaths, a mortality of 9 per cent. However, only 10 of these patients, 30 per cent., developed any signs of mercury poisoning at all. This low incidence of toxicity certainly cannot be due to the treatment employed, for there is no reason to believe that this method of therapy can possibly prevent the occurrence of toxic symptoms if sufficient mercury is absorbed. They have no statistics, therefore, to prove that the method they have outlined is better than any other method of treatment, but simply present it as a logical plan, considering what is known about the disturbed physiology in mercury intoxication.

**NEOARSPHENAMINE.**—*Untoward Effects.*—Ten per cent. of the syphilitic patients treated at the Batavia Hospital suffered from sensitivity to neoarsphenamine, according to P. J. van Putte, (Nederl. tijdschr. v. geneesk. 80: 2103 (May 16) 1936).

The third injection offers the greatest possibility for anaphylactic disturbances. The fatal accidents and the grave disorders have always occurred in cases in which 0.3 or 0.45 Gm. (5 or 7½ grains) was given at the first injection and 0.6 Gm. (10 grains) at the second or third. By administering systematically 0.075 Gm. (1¼ grains) 0.15 Gm. (2½ grains) 0.3 Gm. (5 grains) and 0.45 Gm. (7½ grains) for the first 4 injections at 4-day intervals, he has not had any fatalities among 3000 patients and the treatment from then on was continued with injection of 0.6 Gm. (10 grains) every 5 or 6 days, until 5 Gm. (1¼ drams) of the drug was given.

An injection of an oily suspension of **bismuth hydroxide** containing 0.1 Gm. (1½ grains) of metallic bismuth was allowed regularly **between neoarsphenamine injections**. In serum-negative primary syphilis, 2 of these treatments were given with rest intervals of 1 month and in serum-positive primary syphilis, in primary and in secondary syphilis, 3 of the treatments with an interval of rest between 6 weeks of the second and third. All the patients have been clinically cured and the Wassermann reaction of the spinal fluid and blood have remained negative.

**NICOTINE.**—*Poisoning.*—*Treatment.*—Nicotine poisoning is relatively rare, but it is a potential menace in tobacco factories, especially those which manufacture nicotine products.

The fact that an individual poisoned with nicotine is rarely seen by the physician in time to institute treatment is not

a sufficient reason for a lack of knowledge as to what may be done to save life when the opportunity is at hand.

A. Esser and A. Kuhn state that there is an increasing number of nicotine poisoning cases in recent years, F. E. Franke and J. E. Thomas (J. A. M. A. 106: 507 (Feb. 15) 1936) report 4 cases in a period of 10 years in the city of St. Louis and suggest that in the treatment of nicotine poisoning, **artificial respiration** should be started before the circulation has failed and continued until the muscular paralysis has disappeared, due to the fact that artificial respiration in keeping animals alive after the administration of what would ordinarily be a fatal dose of nicotine is a common laboratory procedure.

According to the literature, it has been used in but 3 cases of reported poisoning in human beings. One was followed by recovery and in the other two, life was evidently prolonged. They believe also that there may be considerable hope of restoring the circulation soon after it has failed by **injection of epinephrine** into the left ventricle and indirect **massage of the heart** through the chest wall.

The circulatory failure that follows nicotine in dogs is not necessarily permanent, but is recovered from promptly if the heart can be started and artificial respiration maintained.

The authors recommend **prolonged artificial respiration** and when the heart has stopped, **intracardiac injections of epinephrine** will be helpful in cases of acute nicotine poisoning.

**NOVOCAINE.**—*Therapeutics.*—The novocaine pack is recommended as therapy in the treatment of fresh accidental *wounds* by M. Fritz and E. Tanner (New York State J. Med. 35: 1217 (Dec. 1) 1935). Cleansing small wounds and suturing them is usually undertaken without anesthesia, since the

pain, although severe, is of such short duration that it can be borne.

Strips of gauze are laid in the wound and a 1 per cent. solution of novocaine is allowed to remain in place for 5 to 8 minutes, or 5 per cent. in 5 minutes for the cleansing and suturing of wounds without pain. The only *contraindication* is the fresh bleeding wound, in which it can be used after hemorrhage has ceased or can be controlled. The area of effective anesthesia was found to extend about 1 cm. beyond the wound edges.

The efficiency of novocaine in the treatment of *simple sprains* was reported on by R. Leriche (*Presse Méd.* 40:280 (Feb. 20) 1932) and W. K. Jennings, (*Illinois M. J.* 69:538 (June) 1936), who found considerable relief in a very short period of time, except in one case in which fracture was demonstrated.

It must be emphasized that this form of treatment is only suitable for *simple sprains*. Joint sprains and sprains with considerable ecchymosis contraindicate its use. He believes that an important adjunct to the injection treatment is a **valgus** or **varus pad**, placed in the heel of the shoe to relax the traumatized ligament.

**OXYGEN THERAPY.**—The Committee on Public Health Relations of the New York Academy of Medicine was requested to prepare a memorandum with information concerning the administration of oxygen. The need for this, according to the request, arises from the fact that there are on the market oxygen tents which are not only inadequate, but may be a source of actual danger to the patient. Acting upon the recommendations of a subcommittee which was asked to investigate this request, the Committee on Public Health Relations has prepared the following report for publication (*New York State J. Med.* 36:828 (May 15) 1936) which

it is hoped will be of aid to physicians and hospital superintendents finding it necessary to use oxygen therapy. Evidence has come to hand which indicates that oxygen therapy is frequently administered in a wasteful and ineffective manner, not only in private practice, but also in the wards of the hospitals. Like all other effective agencies in the treatment of disease, if improperly handled, because of lack of care or proper equipment, this therapy may not achieve the beneficial effects which may reasonably be expected from it.

The purpose of oxygen therapy is to overcome oxygen want, due to some interference with proper oxygenation of the blood, as in *pneumonia*, *coronary thrombosis*, *congestive heart failure*, *emphysema*, or *atelectasis*. In the presence of fever, the metabolism is increased and the oxygen want is thereby increased. If the patient is to be benefited, the amount and concentration of the oxygen employed must be sufficient to compensate for the impairment in the oxygen exchange. It is important that the physician prescribe definitely the concentration of oxygen to be breathed by the patient, just as he prescribes the dose of drugs.

**Concentration.**—The optimum range of oxygen concentration will vary in different patients. In some cases 30 per cent. will be adequate to correct deficiency; in other instances, as high as 70 per cent. may be required. Continuous use of pure oxygen is harmful, but for periods not exceeding 8 hours of the 24, a concentration as high as 90 per cent. has been found safe. In many cases 45 to 50 per cent. is the most desirable concentration.

A 35 per cent. concentration of oxygen in the alveolar air may be achieved by means of a forked nasal tube inhaler or a simple nasal catheter and an oxygen flow of 5 liters per minute. By increas-

ing the flow, even higher concentrations may be obtained. The administration of concentrations between 50 and 70 per cent. is in most instances more satisfactorily obtained by the employment of an oxygen tent. The tent also permits air conditioning.

**Testing Tent Periodically.**—If the tent is to fulfill its purpose, it must be able to maintain the desired oxygen concentration. The possibility of leaks developing in the unit is so great that no tent should ever be used unless its oxygen content is tested at least 2 or 3 times a day and the results of the test recorded. The testing is so simple and yet so essential that no physician should ever employ a tent in his private or hospital practice unless provision is made for periodic testing of the oxygen concentration. This test should not be made immediately after filling the tent with oxygen. If the circulation is directly through the ice, it takes an hour for the concentration of oxygen to be restored to its former height, unless after opening the icebox the flow rate of oxygen is increased temporarily. The blower should be stopped when ice is added or inspected.

**Oxygen Tent Therapy for Adults.**

—In addition to the provision of a prescribed and tested oxygen concentration, 3 other important conditions must be met: (1) For adults a tent should have a capacity of at least 8 cubic feet. (2) The temperature inside the tent should be maintainable at the desired temperature by means of a cooling device. In most patients with fever, a temperature between 58° and 69° F. (14.4° and 20.5° C.) is preferred in winter and slightly higher temperature in summer. Higher temperatures are often desirable for older people and infants. (3) The relative humidity should be maintained between 40 and 60 per cent. When tents are ventilated by a motor blower circula-

tion which passes the air over a cooling medium, such as ice, the humidity will usually be within this range. If the temperature and humidity are not maintained at these comfort levels, the patient will be distressed and the tent will do much more harm than good. The nurse should be instructed to observe and record the temperature within the tent throughout the day and night, or the temperature and humidity may be recorded by an automatic recording device. If the temperature goes above 70° F. (21.1° C.), it generally indicates that there is inadequate cooling and frequently inadequate removal of moisture. This may be due to inadequate circulation of air or provision for cooling.

The carbon dioxide content should not be more than 1.2 per cent. If a minimum flow of 8 liters of oxygen per minute and an oxygen concentration of 50 per cent. is maintained, harmful accumulations of carbon dioxide within the tent will not take place even in the absence of soda lime. If lesser rates of oxygen flow and higher concentrations of oxygen are maintained, especially for adults with fever, soda lime should be used. Because there is no valid indication for continuous stimulation of the respiratory center, mixtures of carbon dioxide and oxygen are not required for most illnesses. For short periods, such stimulation may be of value in such conditions as *carbon monoxide poisoning, drowning, electrical shock, atelectasis of the newborn*, and when there is *shallow breathing*.

Tents which are not equipped with a satisfactory method for cooling and drying the air may be detrimental to the patient and may cause death by heat stroke. No close canopy should be put over a patient's head unless it is equipped with a cooling and dehumidifying apparatus. Tents without blowers are usually unsatisfactory in this climate.

***Oxygen Tent Therapy for Infants.***

—The same general principles apply to tents for infants, except that higher temperatures, and in some instances, higher humidities should be prescribed for very small infants. Smaller tents may be used. It is dangerous to deprive infants of heat by rapidly circulating cool air over them. A tent with an aperture at the top, and to which the oxygen is admitted at the base, may be used, provided it is not placed near an open window or door, where air currents may draw out the accumulated oxygen. The oxygen concentration should be tested and recorded. An umbrella or canopy tent without an air conditioner may be used for infants under two months of age, since such infants produce insufficient heat, water or  $\text{CO}_2$  to permit harmful accumulation of these metabolites.

***Sterilization of Tents.***—All tents should be sterilized after each use by scrubbing inside as well as outside with soap and water. The tents should therefore be made of double-faced material. After scrubbing, the tent should be dipped in a solution of 1 to 10,000 of **bichloride of mercury** for 5 minutes. To prevent incrustation, the tent should be washed down with water after immersion in the bichloride of mercury. In hospital practice an alternate method would be the dipping of the tent in a 70 per cent. solution of **ethyl alcohol** for 5 minutes.

***Fire Hazards.***—1. All tents should be conspicuously stamped "No Flames, No Sparks, Danger."

2. Oxygen gauges should be conspicuously labeled "Danger, Do Not Oil."

3. For the window of the tent, only cellulose acetate or other noninflammable material may be employed. Cellulose nitrate or celluloid should never be used,

because they are extremely inflammable and form dangerous fumes.

***Nasal Catheter or Nasal Tube Administration.***—There are several effective methods of administering oxygen through the nose, employing a nasal catheter or nasal tube inhaler with a calibrated gauge to fit on a high pressure tank. The oxygen must be passed through at least 3 inches of water to prevent drying the mucous membrane:

1. A metal nasal tube inhaler with soft rubber tips which just enters each nostril may be employed.

2. A nasal catheter may be inserted into the nostril for a distance of approximately 3 inches, *i. e.*, up to but not touching the posterior wall of the nasopharynx. Five liters of oxygen generally provide 35 per cent. oxygen in the inspired air. A single catheter may be changed from one nostril to the other if irritation should occur. With a double nasal catheter a slightly increased oxygen concentration is obtained at the same rate of flow. The terminal 1 inch of the catheter should be perforated with 4 holes, in order to prevent a stream of oxygen impinging on one localized area of mucous membrane. The size of the catheter may be a No. 12 French or a somewhat larger calibre if it does not occlude the nasal passage completely.

3. The catheter may be employed in the oropharynx opposite the uvula. When it is used in this position caution must be exercised lest oxygen be passed into the stomach. The catheter should not be placed lower than the uvula. The throat should be sprayed every 8 to 12 hours to prevent drying.

Whereas 4 or 5 liters per minute of oxygen is generally used with the nasal catheter or nasal tube inhaler, higher rates of flow up to 12 liters per minute may be employed if no sensation of discomfort is produced. With the higher rates of flow, larger catheters are re-

quired. When catheters are employed, it is important to make additional holes in the terminal 1 inch.

**Oxygen Regulator and Gauge.**—

Oxygen should be employed in high pressure tanks containing 220 cubic feet or 6000 liters. There is only one kind of oxygen—industrial oxygen. There is no special medical oxygen.

The flow regulator should have 2 gauges, one to indicate the amount of oxygen in the cylinder, and the other to indicate the rate of flow in liters per minute. A variable orifice or float gauge indicates the amount of oxygen actually flowing and is accordingly to be preferred to a dial gauge, which records the pressure against a fixed orifice as liters per minute. The latter type does not indicate that the oxygen flow may have stopped or has been diminished. Bourdon tube type gauges, as well as the pitot tube type gauges, should be tested from time to time by measuring the rate at which the spirometer of a metabolism apparatus is filled at standard pressure and temperature.

CONCLUSIONS. — This statement emphasizes:

1. The effectiveness of the nasal inhaler or nasal catheter.

2. The value of a tent for administering high concentrations of oxygen.

3. The desirability of prescription by the physician of the concentration of oxygen in the oxygen tent.

4. The necessity for repeatedly testing and recording the oxygen concentration within the tent.

5. The necessity for observing the temperature and humidity constantly while the tent is in use.

6. The danger to life involved in employing a tent in which an optimum oxygen concentration is not maintained and in which the temperature and humidity are not observed and controlled,

**PAPAVERINE.**—*Therapeutics.*

—Papaverine, an alkaloid of the opium group, was first advocated for the relief of smooth muscle spasm by Pal, of Vienna. He stated that the drug relaxes smooth muscle without paralyzing it and recommended it in *hypertension*, *angina pectoris*, and for the *abortion of uremic crises*.

W. Denk (München. med. Wchnschr. 81:437 (Mar. 23) 1934) suggested the treatment of *acute occlusion* with intravenous doses of papaverine and stated that the results in 10 cases were equal to those obtained by embolectomy.

G. deTakats (J. A. M. A. 106:1003 (Mar. 21) 1936) reports on the use of papaverine to overcome the initial spasm accompanying an acute *vascular occlusion* and that it may be relieved. In a case of *pulmonary embolism*, it seemed to act as a life-saving measure and in the case of peripheral occlusion it was possible to follow the marked subjective and objective improvement step by step following the early intravenous administration of papaverine. If prompt collateral circulation does not soon develop, embolectomy should be employed.

The injections seem to be a harmless procedure and may actually tide the limb over a critical period or enable the surgeon to operate at a time when without the papaverine, the limb would have been frankly gangrenous. If it is to be of any value, it must be given as soon as the diagnosis is made. Papaverine may be kept on hand in capsules containing  $\frac{1}{2}$  grain (0.03 Gm.) and may be readily dissolved in a 1 c.c. (16 minims) ampoule of physiologic solution of sodium chloride. Slow injection is advisable. The drug should be given in the first 6 hours, combined with **controlled heat**, and **intermittent negative pressure**.

**PARA-AMINO-BENZENE-SULPHONAMIDE AND ITS DERIVATIVES PRONTOSIL AND**

**PRONTOSIL SOLUBLE.**—*Therapeutics.*—The bactericidal properties of para-sulphonamide-benzene-azo compounds were called attention to in 1919 by Heidelberger and Jacobs, of the Rockefeller Institute, but it was not until 1935 that G. Domagk (Deutsche med. Wchnschr. 61:250 (Feb. 15) 1935), after receiving the hydrochloride of 4'-sulphamido-2:4-diaminoazobenzol which had been synthesized by Nietzsch and Klarer, demonstrated its therapeutic activity as the result of experimental studies with mice.

C. Levaditi and A. Vaisman (Compt. rend. Acad. d. Sc. 200:1694 (May 13) 1935) obtained results similar to those of Domagk and in their latest experiments claim that in the subcutaneous administration of a large dose of prontosil in suspension, mice are frequently protected against a fatal dose of streptococcal culture injected 5 to 10 days later. The clinical reports from Germany are favorable to the conquering of hemolytic streptococci infections in *erysipelas*, *puerperal fever*, etc., E. Anselm (Deutsche med. Wchnschr. 61:264 (Feb. 15) 1935) and H. Schranz (München. med. Wchnschr. 82:419 (Mar. 14) 1935) showing it to be well tolerated.

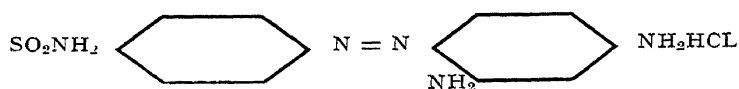
L. Colebrook and M. Kenny (Lancet 1:1279 (June 6) 1936) used the drug in treatment of 38 cases of *puerperal fevers* infected with the hemolytic streptococcus. It was given by mouth

plus the intravenous or intramuscular dose of prontosil. They believe that the drug exercised a definitely beneficial effect manifested by a prompt fall in the temperature, a remission of symptoms, and a reduction in the case mortalities in their series of cases to 8 per cent., as compared with a former series showing 36 per cent. mortality.

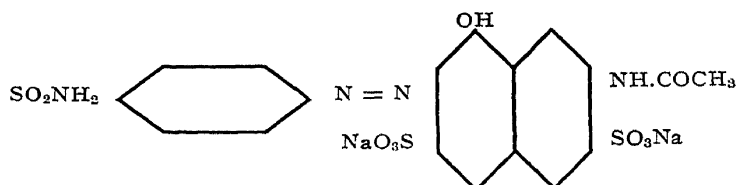
G. A. H. Buttle, W. H. Gray and D. Stephenson (Lancet 1:1286 (June 6) 1936) demonstrated that P-amino-benzene-sulphonamide, commonly known as "*prontylin*," will protect mice against streptococcic infection. They tested the effect of the drug with 6 definite strains of virulent streptococci and found that there was a definite difference in the duration and the number of survivals between untreated and treated mice and considerable difference in the protection against different strains and the optimal dose of the drug. However, protection can be obtained against streptococci belonging to different series. They found that prontylin has the same therapeutic activity as prontosil but is less toxic when given by mouth. The chemical structure of prontosil as given by Colebrook is shown below.

Disodium salt of 4'-sulphamido-phenyl-2-azo-7-acetyl-amino-1-hydroxy-naphthalene-3,6-disulphonic acid.

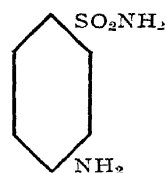
L. Colebrook and M. Kenny (Lancet 2:1319 (Dec. 5) 1936) report on 26 additional cases treated by prontosil by



Hydrochloride of 4'-sulphamido-2:4-diaminoazobenzene. Solubility slight to 0.25 per cent.



Chemical formula of prontosil soluble.



Chemical formula of prontylin—para-amino-benzene-sulphonamide.

Chemical structure of para-amino-benzene-sulphonamide and its derivatives.

injections are given at intervals of 4 hours the first day after operation. The last dose is followed immediately by a low soapsuds enema. This technic has proved effective in preventing *post-operative intestinal atony*. Most gratifying to the patient and the nurse, as well as the surgeon, is the elimination of repeated high compound enemas for the relief of this painful and annoying condition. With this method of administering the prophylactic, peristalsis has been established within 24 hours after operation, whereas prior to its use in abdominal cases, this did not occur until after a period of 48 hours and in some cases after 72 hours. Its use has not been attended by any untoward effects by way of systemic or local reaction, the blood-pressure is not affected, and cardiac action is not interrupted in any way.

#### **SALICYLATES.—Poisoning.**—

**DIAGNOSIS.**—Salicylate poisoning seems to be a clear clinical entity, but one that may be confused with diabetic or renal acidosis. Such a case of poisoning is reported by B. D. Bowen, J. F. Roufa and O. W. Clinger (*J. A. M. A.* 107: 276 (July 25) 1936) and also a case reported by Labbé and his associates (*Ibid.* 106: 55 (Jan. 4) 1936) in which daily doses of 12 Gm. (3 drams) of sodium salicylate without sodium bicarbonate had been given and was followed by a brief period of delirium and restlessness, when the patient became comatose. Respiration was rapid, deep and noisy. Dyspnea appeared to be from central irritation rather than an acidosis. The blood sugar was normal and the alkali reserve was markedly decreased: 18 volume per cent. of carbon dioxide; the pH of the urine was 7.2. Under the administration of **sodium bicarbonate** given intravenously, the alkali

reserve rose and complete recovery from the acidosis ensued. The finding of the violet color reaction in the spinal fluid with ferric chloride may, however, be a differential diagnostic procedure.

#### **SODIUM BENZOATE.—Thera-**

**peutics.**—Administered intravenously, this drug is believed by L. Goldkorn (*Presse méd.* 43: 2094 (Dec. 21) 1935) to have a definite affinity for pulmonary tissue. Patients have noticed a feeling of heat in the chest and head and an agreeable odor which comes on suddenly. As a result of 2200 intravenous injections he feels that the optimum drying and anti-exudation dose corresponds exactly to the dose that produces the aforementioned symptoms. The smallest dose for *pulmonary abscess* is 20 c.c. (5 drams) of a 20 per cent. solution daily. When symptoms of saturation are not produced by this dose, larger doses are indicated. The technic of injection is emphasized. It must be given very slowly and 5 minutes' time should elapse in the administration of 20 c.c. The solution should be made fresh each time with a chemically pure preparation. The injections are given daily and in acute cases, 15 injections are usually sufficient; in chronic cases, 36 are necessary. The injections are continued, however, until the clinical and x-ray signs have entirely disappeared.

#### **SODIUM CHLORIDE.—Thera-**

**peutics.**—The method of treatment termed *rechloridation*, to combat *post-operative complications*, was reported by Max Levy, of Paris, in a meeting of the Académie de médecine (*J. A. M. A.* 106: 2080 (June 13) 1936), who cited some remarkable results from the intravenous administration of 4 per cent. solution of sodium chloride. He stated that there are many deaths following



operations which are difficult to explain if the more common complications are excluded. Recent studies have revealed the existence of a *postoperative toxemia* which may not only be checked in its incipient stages, but the development of which may be prevented by the administration of sodium chloride solution in high concentration. In its mildest form, such a toxemia presents itself in the first few days following operation as a feeling of exhaustion, slight evidences of intestinal paresis, decreased urinary output and lowered blood-pressure. If the symptoms increase, the malaise and weakness become more marked, the tongue is dry, the blood-pressure is lowered, the pulse increased in rapidity, hiccup appears, and the oliguria may progress to almost complete anuria.

The hypochloremia does not express itself by any important sign clinically. Following operation a patient may present a marked hypochloremia and yet seem to be making an uneventful recovery. The increase in residual nitrogen seems to dominate the time of appearance and degree of severity of the symptoms of toxemia. In those presenting the above symptoms, analysis of the blood and urine should be made immediately. The blood examination must include percentage of urea, plasma and globular chloride content and glycemia. The urine examination embraces percentage of urea, chlorides and acetone. All the results can be obtained within 2 hours. The marked decrease or complete disappearance of chlorides in the urine gives the best idea of the degree to which chlorides have been withdrawn from the blood and tissues to be lodged in the operative zone. Treatment should be begun by the administration very slowly of 20 c.c. (5 drams) of a 4 per cent. solution of sodium chloride. The total amount of the chloride to be injected

during the first and following days depends first on the degree of dechloridation. The more marked the diminution of chlorides in the urine, the more sodium chloride should be given. The patient whose symptoms of toxemia are very serious requires a larger amount of sodium chloride, more rechloridation, than a patient with only mild toxemia. The longer the symptoms have lasted, the more sodium chloride is needed. Twenty c.c. is inadequate if all three of these are very marked. Under these circumstances, the first dose should be from 30 to 40 c.c. (1 to 1½ ounces) of the 4 per cent. solution, followed in from 8 to 12 hours by a second one of 20 c.c. (5 drams).

The blood and urine should be examined daily and the treatment continued until the blood chlorides and urea have returned to the normal figure, the quantity of urine greatly increased, and all clinical symptoms have receded. In general, it suffices to give between 20 and 30 Gm. ( $\frac{2}{3}$  and 1 ounce) of sodium chloride the first day, between 10 and 20 c.c. (2½ to 5 drams) the second day, and between 5 and 10 c.c. (1¼ to 2½ drams) the third day.

The results of this rechloridation treatment have been most gratifying, especially following *abdominal operations* in general surgery and after *prostatectomy*.

**SULPHUR.—*Therapeutics.***—A new and successful treatment for the management of *scabies* is outlined as follows by G. V. Kulchar and W. M. Meininger (Arch. Dermat. and Syph. 34:218 (Aug.) 1936).

The patient is directed to take a soap and water bath. After he is thoroughly dry, a 40 per cent. aqueous solution of **sodium thiosulphate** is applied over the entire body except the head and face; particular attention is paid to the areas

between the fingers, to the flexural surfaces of the wrists, and to the breasts, abdomen, buttocks, thighs and external genitalia. Fifteen minutes later, 4 per cent. hydrochloric acid is applied in a similar manner, and 1 hour later the applications are repeated in the same order. The procedure is repeated the next day. On the following day, the patient again bathes and changes to fresh clothing. All bed linen, sleeping garments and clothing previously used are sterilized by boiling for 5 minutes. As the solutions are stable, they may be made up in large quantities and dispensed as needed. Four ounces (120 c.c.) of each solution is sufficient to carry out the treatment.

From their observation in the treatment of patients suffering from scabies in different degrees of severity, the authors conclude that the precipitation of colloidal sulphur on the skin by the inner action of a 40 per cent. aqueous solution of sodium thiosulphate and a 4 per cent. solution of hydrochloric acid provides a simple, effective and economical method of treating scabetic infestations.

Colloidal sulphur used in the form of 2 c.c. ( $\frac{1}{2}$  dram) ampoules is said to contain 10 mg. ( $\frac{1}{6}$  grain) of colloidal sulphur disbursed in a protein-free aqueous medium for intravenous medication. Two c.c. ampoules containing 20 mg. ( $\frac{1}{3}$  grain) of colloidal sulphur suspended in an acid-free olive oil for intramuscular medication were used by S. C. Woldenberg (South. M. J. 28: 875 (Oct.) 1935) in the treatment of 231 cases of *atrophic arthritis*, 5 cases of *hypertrophic arthritis*, and 14 cases of *muscular rheumatism*. Early clinical improvement was shown in the majority of the cases. All the patients except six were discharged from the hospital with a complete arrest of the active symptoms.

Care was exercised in making the diagnosis. All foci of infection were cleared up as far as possible. Protective and corrective treatment was carried out whenever needed. Chronic constipation, an extremely common condition among patients, was corrected and the best nutritional state was secured for each patient by treating anemia, etc. They were placed on a high, low-calorie diet with 50 to 60 gr. protein and the necessary amount of fats according to the patient's caloric requirements. **Exercises**, gradually increasing daily, were given throughout the treatment. Most satisfactory results were obtained from the intravenous medication, the majority of the patients being free from pain after the fifth or sixth injection.

Care must be taken when colloidal sulphur is given intravenously to inject it slowly, to prevent any leakage into the soft tissue, as the latter causes excruciating pain and sometimes sloughing of the soft part at the point of injection. In the more recent cases, the cystine, and sedimentation tests, supported by the clinical observations, have enabled the author to treat very acute cases with doses as high as 30 mg. ( $\frac{1}{2}$  grain) of colloidal sulphur intravenously daily for a full course, resulting in complete riddance of the intense pain within 36 hours of the first injection.

**TANNIC ACID.—Therapeutics.**—The misuse of tannic acid as a result of its obvious benefit in *third degree burns* is pointed out by F. Taylor (J. A. M. A. 106:1144 (Apr. 4) 1936). If the usual 5 per cent. tannic acid solution or any other protein coagulating material is applied to uninjured skin, the outer layers are tanned or "fixed." In mild second degree burns, the action of tannic acid applied to a burned area in which viable islands of the germinal

epithelial cells still survive is not limited to the dead tissue. Many of the epithelial cells which might take part in the repair of the denuded area are also tanned by the treatment. Repair is thus delayed.

Taylor suggests that coagulation treatment of burns be reserved for the severe types and that **bland wet dressings** and **ointments** be used on the greater majority of *second degree burns*.

# PHYSICAL THERAPY

Edited by JOHN S. COULTER, M.D.

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## ELECTROTHERAPY

By JOHN S. COULTER, M.D.

### SHORT WAVE DIATHERMY.

—Mortimer and Osborne consider that there is no evidence to substantiate the claims of specific biologic action of short wave diathermy, and their results show no advantage of one wave length over another for heating purposes.

Unquestionably, the medical profession would welcome proof of the hypothesis that there are brought about additional therapeutic effects aside from the heat produced. Until demonstrable facts supporting this contention are made available, the profession should accept the explanation for the therapeutic action obtained which is substantiated by critical evidence.

L. Hill and H. J. Taylor (*Lancet* 1:311 (Feb. 8) 1936), experimenting with high frequency currents on an excised heart immersed in a small quartz vessel containing Ringer's solution, showed the behavior of a frog heart, cilia and nerve muscle preparation exposed to the 3.4 meter wave length to be exactly the same as when merely heated in Ringer's solution. These authors conclude that the biological effect is due to heat.

In their work with wave lengths of 12 meters and 8 meters, G. W. Wetzel and A. Kiesselbach (*Deutsche med. Wchnschr.* 18 (May 1) 1936) observed the effect of heat on tadpoles. They completely excluded any heat effect by running circulating water through the

glass containers. The animals were radiated twice daily, one-half hour each session. No differences were noted as against control animals. This showed that when the heat is considerably reduced or excluded, there is not noted any damaging nor improving factor on the test animals. These investigators believe, therefore, that the chief cause of the biologic action of the short wave is the heat that is produced by the energy exchange.

J. S. Coulter and H. A. Carter (*J. A. M. A.* 106:2063 (June 13) 1936), in their investigations on the heating of live human muscle and fat, found there were no significant differences in the use of 6, 12, 18 and 24 meter wave lengths when using the cuff technic of the electric field method and no significant differences in the use of 12, 18 and 24 meter wave lengths when using the coil technic of the electromagnetic field method.

In summarizing their investigations, W. E. Curtis, F. Dickens and S. F. Evans (*Nature* 138:63 (July 11) 1936) state in regard to specific action: "If such an effect exists, it should be possible for the discoverers to describe at least one clear-cut experiment which could be repeated by other workers. In the absence of such evidence we consider that the great mass of inconclusive observations which has been presented is a very insecure foundation for the

rapidly growing belief in specific short wave therapy. Whilst the possible existence of specific actions of ultra short waves cannot be denied, in our opinion such effects have not as yet been adequately demonstrated. We therefore find ourselves in agreement with the conclusions of Mortimer and Osborne."

The lack of specific action of different wave lengths in heating human tissues has not only been proved in studies on the human thigh by Coulter and Carter, but also in pelvic heating experiments. In a recent study by J. S. Coulter and S. L. Osborne (*Arch. Phys. Therapy* 17:135 (Mar.) 1936) of vaginal and rectal temperatures, utilizing 9, 15, 16.4, and 24 meter short wave medical diathermy with electric field, no significant differences in heating effects were found. When using electromagnetic induction with a 24 meter wave length, a temperature rise of approximately  $1.5^{\circ}$  to  $2^{\circ}$  higher was found than when using the electric field. A study of this data indicates that the rise was not due to the difference in wave length, but a difference in the method and technic of application.

E. A. Horowitz, S. Gottesman, D. Derow and M. Schwartzchild (*Ibid.* 17:422 (July) 1936), using 9 different apparatus with wave lengths varying from 6 to 18 meters, agreed with above findings. With a 6-meter electric field short wave medical diathermy using

metal vaginal electrodes, they obtained a rectal, bladder, and vaginal temperature of approximately  $106^{\circ}$  F. Apparently this was not due to the difference in wave length, but to the technic employed.

Using an electric field of wavelength 6, 12, 15, 18, and 24 meters, J. S. Coulter and S. L. Osborne (*Ibid.* 17:679 (Nov.) 1936) found no significant differences in the heating of live human muscle and fat. When using electromagnetic field of wave lengths 12, 18, 24, and 25 meters no significant differences in the heating of muscle were observed.

In the study of tissue heating of human thigh, using electric field and air-spaced electrodes, the amount of heat is dependent on the method of application, the size of the electrodes, the distance of the electrodes from the skin, the capacity of the skin, and the patients' tolerance.

**ELECTRICAL MUSCLE STIMULATION.**—A. Myerson (*J. A. M. A.* 105:1565 (Nov. 16) 1935) emphasizes the value of the use of strong galvanic muscle stimulation in *hysterical paralysis*.

H. Chor (*Physiotherapy Rev.* 16:35 (Mar.-Apr.) 1936) states that early stimulation of the paralyzed muscles in *infantile paralysis* has been found harmful. He has confirmed this clinical observation in recent experiments on animals.

## EXERCISE AND MANIPULATION

By JOHN S. COULTER, M.D.

**CERVICAL ARTHRITIS.**—The clinical features of arthritis of the cervical spine are described by S. S. Hanflig (*J. A. M. A.* 106:523 (Feb. 15) 1936). Rigidity is present and its extent varies with the degree of muscular spasm, the extent of ligamentous ossification, and

the presence of osteophytes or hypertrophic changes. In the acute or infectious variety the rigidity is due to muscular spasm. In more advanced cases, ligamentous ossification is the cause. In far advanced cases, the osteoarthritic or hypertrophic variety, the

rigidity is due to osteophytes growing at the margins of the vertebral bodies and on spinous and transverse processes.

Hanflig believes that if the arthritis is *subacute* or *chronic*, and this is the usual type, **stretching** and **manipulations** are indicated. An overhead hook into which can be attached a block and tackle Sayre's sling suspension apparatus is needed. The patient is seated on a chair under the apparatus. The Sayre's sling, well padded at the chin and occiput pieces, is applied. Traction is applied and is continued until the patient's buttocks swing freely, when rocked, just above the seat of the chair. While the patient is suspended in the air, the shoulders are held by an assistant, and the head and Sayre sling are rotated to the left and right. The patient is then lowered and rested for a moment or two, and then the entire procedure is repeated.

A Thomas collar is made and applied, to be removed only for the hot fomentations to the neck that follow each treatment.

It has been customary to carry out this treatment 3 times the first 2 days, twice a day thereafter, and then spaced out as seems advisable. The number of treatments varies tremendously and is determined by the progress of the disorder. Similarly, the period of wearing the Thomas collar varies.

As soon as the pain begins to go, active **graded exercises** in rotation, flexion and extension are advised. The patient is advised to return at stated long intervals for inspection, at which time occasional neck stretchings and manipulations are advised if any recurrence of pain or increase in limitation of motion is observed.

This treatment can be used as a diagnostic test, because in most cases in 2 or 3 days there is beginning relief of pain. It is effective as a treatment, probably

because it mobilizes adhesions, breaks up bridging of fine calcifications, and relieves muscle spasm, thereby contributing to a better carriage of the cervical spine.

**SUBACUTE AND CHRONIC FIBROSITIS.**—Although the symptomatology of fibrositis has of late been very fully dealt with in medical literature, T. S. Wilson (Brit. M. J. 1:298 (Feb. 15) 1936) believes that general recognition does not seem to have been given to the possibility of effective treatment of its painful *subacute* and *chronic* stages by **forcible breaking down** of the **nodules and cords** to which much of the pain that characterizes the condition is due.

Fibrositic nodules are not due to a deposit of inflammatory tissue, but to the agglutination of normal fibers of either fibrinous or muscular tissue by a minimal amount of inflammatory material due to some preëxistent inflammation. When a nodule is forcibly broken down, it can in the course of a few minutes be made to disappear entirely in a manner which would not be possible if the bulk of the nodule were due to inflammatory deposit and not to normal tissue under abnormal conditions.

Fibrositic nodules contain a large amount of toxin, presumably streptococcal in type, which is set free in the circulation when the nodule is forcibly broken down. Care must, therefore, be taken as to the number of nodules broken down at any one sitting, otherwise a definite reaction may result, as is the case with vaccine treatment. The breakdown of fibrositic nodules must, therefore, be regarded as a form of vaccine treatment, and its adoption regulated by the same principles as those which govern the injection of a vaccine.

The fibrositic nodules contain living microorganisms, presumably streptococci,

and not simply toxin. This is shown by the clinical observation that nodules which, judging by their hardness and by the history of the case, must have been in existence for many months or years are, when broken down, quite as liable to give rise to a reaction as nodules of more recent origin. The results of manipulative treatment seem to prove that the pain to which fibrositic nodules give rise is due to strained muscular fibers, and not to irritation of sensory nerves.

The object of manipulative treatment must be to burst the nodule by a sudden and very forcible pressure of the fingertips, which is calculated to tear asunder the agglutinated fibers of which it consists. This can be done by combining a very rapid to-and-fro rolling movement with the pressure. This treatment can only be adopted effectively in situations where the cord or nodule can be compressed against subjacent bone, and also where no structures occur, such as nerves or tendon sheaths, that might be damaged by the force used.

Occasionally a large nodule may be found in the central portion of a muscle. Such a nodule can, however, be broken up by the rolling movement already described, apart from the use of any great force. The rolling pressure must be applied at either end of the date-stone-shaped nodule where the free fibers enter it. With a little patience the nodule can gradually be broken down by rolling the free fibers against one another at the point where they become agglutinated, and thus separating them from the mass and lessening its size.

**BREATHING EXERCISES IN ASTHMA.**—J. L. Livingstone and M. Gillespie give their ideas on breathing exercises in asthma. Of 75 cases of asthma treated for 1 year with exercises, good clinical results were obtained in 52, improvement in 12 and no improvement in 11 cases.

The treatment of asthma by physical exercises has proved so successful that the Asthma Research Council, King's College, London, has issued an illustrated pamphlet on it. The following are the essential points of these exercises:

1. Before commencing the exercises, the patient should blow the nose on a handkerchief to ensure a clear air-way.
2. As the object of the exercises is to empty the lungs, each exercise should begin with a *short* sniff-in through the nose, followed by a *long* breathe-out through the mouth, making a whistling noise with the lips. This noise fixes the patient's attention on blowing out as long as possible.
3. When breathing *in*, the patient must learn to keep the upper part of the chest still, so that the breathing is performed mainly by the abdominal muscles and diaphragm. When breathing *out*, the abdominal wall should contract, sinking in towards the spine; by allowing the abdominal wall to relax or sag out, the next breath is drawn into the lungs automatically. All exercises should finish by breathing out with the abdomen contracted.
4. The patient should breathe out sufficiently to hear the wheezing noises in the base of the lungs. This may cause coughing and increasing wheezing, but should be gently persevered with. The patient should rest for a minute or two between each exercise.
5. To begin with, the exercises should be done very gently with plenty of rest. When the patient is "tight on the chest," he should do them in the reclining position, lying back on the pillows with the knees comfortably drawn up.

## FEVER THERAPY BY PHYSICAL MEANS

FRANK H. KRUSEN, M.D., and DANIEL H. AUTRY, M.D.

In reviewing the literature of the past year, there is found a continued wide interest in physical agents for the pro-

duction of therapeutic fever. While the apparatus for its production has not been altered materially, studies of the

technic of administration and of the clinical results have been very extensive.

**Methods of Treatment.**—The greatest interest is directed toward study of 3 methods of producing fever, *i. e.*, air-conditioned cabinets, short wave diathermy devices, and electric blankets.

**RADIANT HEAT.**—*Air-conditioned Cabinets.*—The past year has seen a great deal of excellent work with this particular type of apparatus. Although these cabinets do not produce a rise in body temperature by direct application of radiant heat to the surface of the body but rather by the heating of circulated air which is blown over the body, they may still be classed as radiant heat devices. Hyperpyrexia is produced by the heated air. The construction of the cabinets has been described by various investigators: F. H. Krusen; H. W. Kendell, W. W. Webb, W. M. Simpson and E. C. Sittler. This type of device is elaborate, requires a skilled team of workers for its operation and is not on the market at present. There are approximately 55 of these cabinets (which have been given the name “*Kettering Hypertherm*”) scattered throughout the country at various medical centers for the purposes of clinical research. From a technical standpoint, so far as the production of prolonged high fever is concerned, the reports on the efficacy of this device have been uniformly favorable.

R. F. Atsatt and L. E. Patterson (Arch. Phys. Therapy 7:108 (Feb.) 1936) have described a device for the production of artificial fever by means of conditioned air which they say can be constructed by any competent hospital engineer at a cost that is considerably under \$100. They described this device in detail so that it could be reproduced by following their diagrams and description.

**Luminous Heat Cabinets.**—Of the various luminous heat cabinets, the one described in 1935 by F. W. Bishop, E. Lehman and S. L. Warren probably is as satisfactory as any. These cabinets do not possess the features of air humidification and air circulation found in the previously mentioned cabinets. These investigators stated that “humidity control of the air in the radiant energy cabinet was investigated and was found to be of little benefit in the set-up described, especially in view of the complications it imposed.” It has been the REVIEWERS’ experience, however, that the lack of proper humidification is something of a disadvantage. There is one other disadvantage of this cabinet as described by the men who devised it and that is, that it is insufficiently insulated. However, Bishop, Lehman and Warren stated that the radiant heat method described seemed to be the most convenient and economical one in their experience. They gave the cost of their cabinet as approximately \$150 and included in their article an excellent description of its construction.

It is likewise worth noting that C. A. Johnson, Osborne and George Scupham (Am. J. M. Sc. 190:485 (Oct.) 1935) believed that the ordinary electric light cabinet was the safest method for the production of artificial fever by physical means.

C. A. Neymann (Fourteenth Annual Meet. Acad. Phys. Med., Boston (Oct. 20-22) 1936) has described a new type of “air-conditioned cabinet” which he proposed to use in conjunction with a high-frequency induction coil in the production and maintenance of artificial fevers. He recommended lower cabinet temperatures and higher humidification than have been used by other workers.

**Nonluminous Heat Cabinets.**—There have been marketed by various manufacturers cabinets which somewhat resemble



the one described by Bishop, Lehman and Warren, with the exception that the cabinets are heated by resistance heat coils rather similar to those found in the familiar household electric heater. Some of these devices have been humidified by means of a water trough within the cabinet. This method of humidification, however, is most unsatisfactory. None of these devices has yet been accepted by the Council on Physical Therapy as being satisfactory for the production of fever.

**ELECTRIC BLANKETS.**—Various kinds of electric blankets, frequently constructed like a large sleeping bag, have been used for fever therapy. They are less expensive than the cabinets, but their great disadvantage is that the patient is closely confined by such blankets. R. H. Kuhns (Arch. Phys. Therapy 17:167 (Mar.) 1936), after 4 years of trial, expressed the opinion that the electric blanket is the "simplest and safest form of fever producing agent." These electric blankets, however, may be used satisfactorily only in those cases in which a fever of not more than 103 to 104° F. (39.4° to 40° C.) is required. For higher temperatures than this, they are not at all satisfactory, and as has been said, patients are made most uncomfortable by them.

**HIGH FREQUENCY ELECTRICAL METHODS.**—*Conventional (or Long Wave) Diathermy.*—This method of treatment, first described in 1929 by C. A. Neymann and S. L. Osborne, is still being used by many workers, but it has been replaced, to a certain extent, by other devices that have been developed more recently. With this method an ordinary diathermy machine is used, and large electrodes are placed in such a manner that a large portion of the body is traversed by the high frequency current. Diathermy plates may be placed on the back and on the anterior surface of

the trunk, or it is possible to apply cuffs to the extremities. Another method is to apply a plate to each foot and to keep the legs separated, so that the current must travel the entire length of each leg to complete the circuit. The patient is then covered with some form of insulation to prevent dissipation of the heat produced in the body by the high frequency current. This insulation may be produced by blankets, a zipper-bag, or an insulated cabinet.

*Short Wave Diathermy.*—The short wave diathermy machine is somewhat similar to the conventional diathermy machine, with the exception that the oscillations of current are much more rapid (conventional diathermy machines produce approximately 2,000,000 oscillations per second, as compared with short wave diathermy machines, which may produce 100,000,000 or more per second). Heating of the patient's body may be produced either by the induction coil or by the condenser plate method. With the induction coil method a coil of heavily insulated wire or ribbon is attached to the machine. The coil is either wound around the patient's body or placed close to the surface of his body in the form of a large pancake and he is then heated by means of the high-frequency electromagnetic field that is produced. Insulation of the patient's body is accomplished by means of blankets, a zipper-bag, or an insulated cabinet. One such method was described in 1935 by H. E. Kimble, H. J. Holmquest and J. G. Marshall.

With the condenser plate method, essentially the same technic is used, with the exception that the coil is replaced by two large condenser plates which are placed on each side of the patient in such a manner that a considerable portion of his body is within an electrostatic field between them. The patient's body is then heated by the high-fre-

quency current that passes between these two plates. Insulation of the patient's body is accomplished as previously mentioned.

One of the *disadvantages* of short wave diathermy is the tendency for the production of a burning sensation on the moistened skin when the patient begins to perspire. In addition, when the patient assumes a posture in which two surfaces of the skin are touched together very lightly, burning is likely to occur at the site of contact. For this reason, a number of investigators have abandoned the use of high-frequency currents in favor of some form of external heat cabinet (Kendell, Webb and Simpson and Bishop, Lehman and Warren).

**HYDROTHERAPEUTIC METHODS.**—*Hot Tub-baths.*—The production of fever with hot baths, which was described by Phillips in 1883, by Schamberg and Tseng in 1927, and by Mehrtens and Pouppirt in 1929, is still being used very successfully by some investigators. Although prolonged hot tub-baths are quite enervating, nevertheless, the patient's temperature may be raised rather rapidly, and it may be maintained at a fairly high level for from 1 to 2 hours by this method alone. The REVIEWERS have used this method to induce artificial fever with satisfactory results. After the temperature has been increased, it can be maintained by means of blankets, or, better still, by means of a very simple radiant-heat cabinet. The simple tub-bath is less expensive and less complicated than the aforementioned high-frequency electrical methods of producing fever. As a rule, the temperature may be raised more rapidly in a simple tub-bath than can be done by means of either the conventional or short wave diathermy. It seems likely that, as physicians continue their search for simpler and better methods of producing artificial fever by physical means, they will use this

“hot bath induction-radiant heat cabinet method” more frequently than at present.

*Hot Spray Baths.*—The nude patient is placed in a cabinet in the prone position with his head protruding from one end, very much in the fashion employed in air-conditioned and other types of heat cabinets. He is then sprayed with a series of very fine jets of nebulized, very hot water, the temperature of which is controlled by means of a thermostat. This spray cabinet will produce a rapid rise in bodily temperature if the temperature of the water can be maintained at the proper degree. One supposed advantage of this method is that the thermostat can be switched momentarily to cold. The brief spray of cold water will produce a refreshing effect on the patient; at the same time, if the switch to cold is made for a very brief time only, there will be a rise in the bodily temperature instead of a decrease. Apparently the momentary contraction of the peripheral capillaries caused by the cold spray drives the warm surface blood into the splanchnic regions and thus produces a further and more rapid rise in the systemic temperature. By this method, therefore, it seems to be possible to raise the temperature somewhat more rapidly than with the ordinary heat cabinet; it is doubtful, however, whether a too rapid rise of temperature is wise. The chief detriment to the use of this device is that the operator must depend on a general water supply as the source of heat, and it seems rarely possible to obtain a constant flow of sufficiently hot water. In the experience of the REVIEWERS with this type of machine (probably because of an unsatisfactory source of water supply), they were unable to procure the smooth, prolonged high temperature curves attained with radiant heat and air-conditioned cabinets. It would seem, however, that this device is satisfactory for the induction of

temperatures of 104 or 105° F. (40 or 40.5° C.); after this, the temperature may be maintained with blankets or with a simple, radiant heat cabinet.

#### OTHER CONDUCTION HEAT METHODS.

—N. N. Epstein and M. Cohen have devised a simple method of inducing hyperpyrexia by *wrapping the patient in blankets and rubber sheeting*. With this method no source of heat other than the natural heat of the body is utilized. However, a period of 4 or 5 hours is necessary simply to raise the temperature to 104° F. (40° C.), which would seem to subject the patient to an unnecessarily long period of discomfort before the required high temperature is achieved. If this method is to be used, it would seem expedient to use at least a few *hot-water bottles* incorporated in the patient's wrappings in order to make the induction of fever more rapid.

#### *Hot-water Bottle and Planket Method.*

—Hadden and Wilson, in 1933, described this method, which is still used quite frequently. The patient is simply wrapped in a number of thick blankets and surrounded by hot-water bottles. The great disadvantage of any blanket method rests in the fact, as has been indicated, that nearly all patients are made extremely uncomfortable by confinement of their limbs by the necessarily tight wrapping of so many heavy coverings.

#### *Technic.*—SELECTION OF PATIENTS.

—Emphasis cannot be laid too strongly on the need for careful selection of patients. Patients should be selected with care, being subjected to a careful physical examination before treatment, and all cases of even moderate hypertension, cardiac disease, or debility rejected. Functional disorders of the heart need not necessarily be a contraindication to fever therapy, according to A. U. Desjardins, L. G. Stuhler, and W. C. Popp (J. A. M. A. 106: 690 (Feb. 29) 1936), and under

satisfactory control, patients with diabetes may also be accepted. While pulmonary tuberculosis may not be a contraindication *per se*, the associated respiratory involvement may prevent the satisfactory rise and maintenance of a proper level of temperature. Fever therapy is not contraindicated by the presence of subacute carditis or of inactive rheumatic heart disease and it may even be of benefit in such cases, according to L. P. Sutton and K. G. Dodge (J. Lab. and Clin. Med. 21: 619 (Mar.) 1936). In general, it might be said that any contraindication to major surgery is likewise a contraindication to this type of therapy.

PERSONNEL.—A carefully trained team of nurse-technicians and physicians is essential for the safe conduct of fever therapy. A competent physician, familiar with all possible reactions, should be at hand at all times during treatment. Nurse-technicians who have had at least a month's special training in this type of nursing should be employed in the actual administration of the treatment. In this connection J. E. Benjamin has declared, "The percentage of coöperative patients is directly related to the expertness and the tact of the nurse in charge," and he is convinced that failure to achieve a measure of success with fever therapy in many institutions arises from the fact that the attendant nurses have not been adequately trained and imbued with the psychologic principles that are essential to effective treatment. For these reasons fever therapy is necessarily confined to institutions.

*Management of Patients During Treatment.*—W. C. Popp stated: "Fever therapy is tolerated in a number of ways by a variety of patients. The average individual who has been told about the type of treatment and who understands it to some extent tolerates it very well. On the other hand, a certain group of

high-strung temperamental individuals tolerate it rather poorly." The most common *untoward results* during fever therapy are headache, restlessness, nausea, vomiting, tetany, muscle cramps and pain. Heat prostration may occur. Periods of unconsciousness may occur, but are rare, and consciousness is regained, as a rule, as soon as the temperature is lowered. Restlessness frequently requires sedation, which may be repeated every 2 or 3 hours. Nausea and vomiting occur more frequently in women and may be controlled by intravenous injection of 500 to 1000 c.c. (1 to 2 pints) of 10 per cent. **dextrose** and 1 per cent. **sodium chloride solution** during the treatment (A. U. Desjardins, L. G. Stuhler and W. C. Popp: *loc. cit.*). *Tetany*, which resulted from hyperventilation, may be readily corrected by the injection intravenously of 10 c.c. ( $2\frac{1}{2}$  drams) of **calcium gluconate**. M. J. Lepore, after a careful study of the metabolism of chloride and water, concluded that: (1) It is of the utmost importance to maintain the patient's intake of **fluid** at a high level. For the average 6- to 7-hour period, a total intake of between 90 and 100 c.c. per kilogram of body weight (an average of 3000 to 4000 c.c.—3 to 4 quarts) has been found effective. (2) An intake of **sodium chloride** of at least 20 Gm. (5 drams) will cover the chloride loss in sweat for the average treatment. This may be accomplished by having the patient drink from 3 to 6 liters (quarts) of 0.3 or 0.6 per cent. **solution of sodium chloride (iced)** during the session of fever. The patient may also have **milk, sweetened tea, orange juice, lemonade**, etc.

In those cases in which patients are treated by air-conditioned cabinets, the condition of the *skin* should be observed frequently. The feet and legs are protected by terry-cloth coverings from the beginning of treatment. If an area of

reddening appears on any part of the body, it is protected from the hot air by means of a towel. If the reddening becomes more prominent, a cold cloth or piece of ice may be applied. By observing such simple precautions and by raising the patient's temperature gradually (60 to 90 minutes) severe burns can usually be avoided, according to Desjardins, Stuhler and Popp (*loc. cit.*).

Episodes of *delirium* during a session of fever may be a not uncommon occurrence, and they tend to reflect the patient's dominant interests, habit patterns, and other personal characteristics. In the report of F. G. Ebaugh, C. H. Barnacle and J. R. Ewalt (Am. J. Psychiat. 93:191 (July) 1936) of 331 delirious episodes occurring among 200 patients in 1324 sessions of fever, the height and duration of the fever and the administration of sedatives did not apparently affect the clinical picture. A considerable number of this series (21 per cent.) had only one attack of delirium, indicating that anxiety was frequently gone after the first treatment. In the experience of the REVIEWERS, delirious episodes have been very infrequent, the great majority of patients tolerating treatment with little apprehension.

*Dosage*.—P. S. Hench, C. H. Slocumb and W. C. Popp stated that as a result of studies of the thermal death time of gonococci, the correct dose of fever for *gonorrheal infections* has been more properly established. The majority advocate the administration of about 5 hours of fever at 106° to 106.8° or 107° F. (41.1° to 41.5° or 41.6° C.) rectal temperature. For *acute gonorrheal arthritis*, the majority have administered about 1 to 4 sessions of fever, with an interval of 3 to 7 days between sessions. S. L. Warren, C. M. Carpenter and R. A. Boak first determine the

thermal death time of the particular strain of gonococci in each case, then give the patient one session of fever for a period equal to that particular thermal death time.

J. J. Sheldon, in discussing the treatment of intrinsic intractable *asthma* by means of fever therapy, described his method of treatment as follows:

"When fever therapy was first started in these patients they were routinely given a course of 4 treatments at 7-day intervals. The bodily temperature was maintained at 104° to 105° F. (40° to 40.5° C.) for a period of 5 to 6 hours by means of a Kettering hypertherm. It was observed that relief was often obtained after the first or second treatment; therefore, more recently the number of treatments has been reduced to one or two. The interval between treatments, if more than one is given, has been changed to 3 days. For those patients who have had a return of their asthma, we are now giving one treatment, with elevation of body temperature to 105° to 106° F. (40.5° to 41.1° C.) for 6 hours."

K. Phillips and S. Shikany, in discussing the treatment of *bronchial asthma*, were of the opinion that 10 treatments should be the minimum for a course. It would appear that 12 to 15 are still better, but apparently there is no improvement beyond this number. Two treatments a week are preferable to one. Some of their best results, however, were obtained by treatments once weekly. Temperatures maintained above 105° F. (40.5° C.), rectally, were found to have no advantage over those ranging between 102° and 105° F. (38.9° and 40.5° C.). Temperatures sustained for 4 hours were found to produce results comparable to those obtained with longer periods of fever.

W. M. Simpson (Brit. J. Ven. Dis. 12:133 (July) 1936) regarded a mini-

mal course of artificial fever therapy for patients with *syphilis* as consisting of 50 hours of a sustained temperature between 105° and 106° F. (40.5 to 41.1° C.), rectally, to be administered in conjunction with 30 injections of an anti-syphilitic agent. In discussing the treatment of *ocular syphilis*, A. M. Culler described his technic as follows: "Utilizing a comparatively simple, safe, controlled air-conditioned apparatus for fever induction and maintenance (**Kettering hypertherm**) 50 patients with various manifestations of ocular syphilis have been treated with approximately 50 hours of fever above 105° F. (40.5° C.), in 10 weekly sessions of 5 hours each. A course of 30 injections of **bismuth arspenamine sulphonate (bismarsen)** was given in conjunction with the fever treatments."

For the treatment of *chorea*, T. G. Schnabel and F. Fetter favored a series of 4 treatments, each lasting 3 hours at a temperature between 105° and 106° F. (40.5° and 41.1° C.), given twice weekly. C. A. Neymann, M. L. Blatt, and S. L. Osborne (J. A. M. A. 107:938 (Sept. 19) 1936) obtained very satisfactory results from their method of treatment; it averaged 4 sessions per patient, was given twice weekly at a temperature of 103.5° to 105° F. (39.7° to 40.5° C.) for 8 hours. In the REVIEWERS' experience, daily sessions of fever lasting 3 hours at 103° to 104° F. (39.4° to 40° C.) for 6 treatments have produced favorable results in such cases.

**Effects of Fever Therapy.**—A summary of the numerous studies on the effects of fever produced by physical means indicates that the following changes are produced.

**BACTERICIDAL EFFECTS.**—*Neisseria gonorrhoeæ* generally is destroyed at a temperature of from 106° to 107° F. (41.1° to 41.6° C.) in from 6 to 27 hours, according to R. A. Boak, C. M.

Carpenter and S. L. Warren. In a high percentage of cases of *syphilis*, dark-field illumination will fail to reveal the presence of *Spirochaeta pallida* after the patient has been treated with fever induced by physical means (Epstein and Cohen). Following exposure to temperatures within physiologic ranges, no cultural changes, *in vitro*, are noted in *Mycobacterium tuberculosis*, *Streptococcus haemolyticus*, or *Streptococcus mitior* (G. R. Duncan and E. S. Mariette). The last-named organism appears to resist, *in vivo*, any degree of heat possible for the human body to tolerate (H. A. Freund and F. B. Watts). *Micrococcus catarrhalis*, *Haemophilus conjunctivitis*, *Haemophilus influenzae*, *Brucella abortus*, *Escherichia coli*, *Eberthella typhosa*, *Streptococcus haemolyticus*, *Streptococcus viridans*, and *Diplococcus pneumoniae* (type 1 and 3) usually resist *in vitro* temperatures of 107° F. (41.6° C.) for a period of 24 hours; an occasional strain shows some reduction in numbers (L. Thompson, C. Sheard and N. Larson: Proc. Staff Meet., Mayo Clin. 11:319 (May 13) 1936).

EFFECTS ON CIRCULATORY SYSTEM.—The pulse and circulatory rates are increased, according to K. Phillips and S. Shikany. The minute volume output of the heart is increased and the velocity of the blood may be increased as much as 400 per cent. (W. M. Simpson). There is an initial increase followed by a decrease in pulse pressure (A. U. Desjardins and W. C. Popp). There is a marked increase in pulse volume in the fingers in all types of artificial fever, with the exception of that caused by foreign protein. It has been suggested that the vasodilation which occurs during fever produced by foreign protein is possibly of central origin, whereas that which occurs in artificial fever induced by external heat, with consequent pre-

vention of loss of heat, is chiefly of peripheral origin.

The maximal increase of circulation in artificial fever occurred, in general, at temperatures between 103° and 104° F. (39.4° and 40° C.) (Johnson, Osborne and Scupham: *loc. cit.*). Alterations in the electrocardiogram are not uniform. While the amplitudes of the contractions are decreased, as a rule, the changes are not permanent, so it cannot be inferred that fever therapy has any harmful effect on the heart, according to H. Vesell and W. Bierman (Am. J. M. Sc. 191:484 (Apr.) 1936).

There is no change in the volume, or only a slight concentration, of the blood and no change occurs in the viscosity of the blood when the intake of fluids is encouraged (Hench, Slocumb and Popp; and J. F. Simon: J. Lab. and Clin. Med. 21:400 (Jan.) 1936). The visible capillaries of the nail beds are increased in number and size. The erythrocyte count is generally not changed. An initial decrease and a subsequent increase in the number of leukocytes occurs. There is a relative and an absolute decrease in the number of lymphocytes. The hematopoietic response is characterized by consistent leukocytosis, with delivery of polymorphonuclear neutrophils of increasing immaturity. Destruction of lymphocytes occurs and there is probably some destruction or redistribution of monocytes. A shift of the neutrophilic granulocytes to the left and the presence of clasmocytes in the peripheral blood (which are outstanding in malaria) are not seen in cases in which fever is produced by physical means (M. M. Hargraves and C. A. Doan).

There is either no change in the nitrogenous constituents (urea, uric acid, creatinine), or there may be only slight increase, if any, in the concentration of the blood (Hench, Slocumb and Popp).

There is a nearly consistent increase in the creatinine clearance in contrast to wide variations which occur in infections (W. H. Grant and G. Medes). There is either no change in the nonnitrogenous constituents (sugar, phosphorus, lipids, calcium), or only a slight increase if there is an increase in concentration of the blood. No significant decrease occurs in the lipids of the plasma such as is seen in acute infections (A. V. Stoesser and I. McQuarrie). There probably is an alteration in the acid-base balance of the blood in the direction of slight alkalosis (W. H. Danielson and R. M. Stecher). Marked alkalosis may be noted (M. J. Lepore). Opinions vary as to the effect on the chlorides; some writers claim that there may be a marked decrease (Desjardins and Popp), while others state that there is no significant change (Phillips and Shikany). If salt or weak saline solution is administered by mouth during treatment, the blood chlorides drop very little; if no sodium chloride is administered and if there is profuse sweating, a drop in the chlorides is to be expected. The oxygen content and oxygen-combining power of venous blood are increased (Hench, Slocumb, and Popp). Opinions also vary as to the effect on the agglutinins, but the agglutination titer is generally within normal limits (R. W. Jung: Arch. Phys. Therapy 16:397 (July) 1935). The complement fixing antibodies are temporarily diminished, but there is no change in the opsonic index (L. G. Hadjopoulos and W. Bierman).

**OTHER EFFECTS.**—Examination of the *gastric contents* reveals a sudden decrease in the amount of chlorides and an increase in the amount of lactic acid (Hench, Slocumb, and Popp). The *urine* is increased in amount, but temporary oliguria generally occurs. The reaction of the urine is unchanged, or the urine is slightly alkaline and its specific gravity

is increased (Phillips and Shikany, and W. J. Egan and R. Piaskoski). The *basal metabolic rate* is increased approximately 7 per cent. for each degree of fever induced (Hench, Slocumb, and Popp). Cold fluids, taken by mouth, produce fluctuations in the *gastric temperature* but do not appreciably affect the general temperature, according to E. C. Sittler. Comparison of the temperatures in the median antibrachial vein, rectum, uterine cervix, Hunter's canal, bladder, and spinal canal indicate that records of the rectal temperature provide an accurate index of the temperature of the deep tissues (E. C. Sittler). After each individual treatment there may be a temporary loss of weight, due to loss of fluids (unless sufficient fluids are taken by mouth). However, this loss is quickly regained and after a course of fever therapy a patient usually retains his original weight or may even gain weight.

**COMPLICATIONS.**—Mention has already been made of the reactions that may occur during a session of fever, such as headaches, nausea, vomiting, tetany and abdominal cramps. Nausea and vomiting may also be present the evening after treatment, although it is usually relieved within 24 hours. Herpetic lesions on the lips and in the mouth, nose and pharynx may be quite severe and make drinking and eating difficult for a time. However, such severe lesions are unusual, and the less marked lesions tend to clear up even though subsequent treatments are continued at the regular intervals. Occasionally, superficial burns, especially of the arms, occur. However, these do not, as a rule, interfere with subsequent sessions of fever and they will be avoided in practically all cases if the precautions previously mentioned are carefully followed.

The most serious complications are the *collapse*, with possibly a fatal out-

come, that may occur during treatment in spite of careful pre-treatment examination and even though the condition of the patient is apparently good during treatment. In cases of collapse, the usually accepted treatment for shock is administered. Besides taking care that the temperature does not rise above safe physiologic limits, serious consequences may be avoided, as a rule, by discontinuing treatment whenever any of the following conditions are found: (1) a systolic blood-pressure less than 80 mm. of mercury; (2) a pulse pressure of less than 20 mm.; and (3) a pulse rate of 160 or more for more than 30 minutes. Often in the presence of these conditions, **cooling the patient momentarily** may result in improvement lasting throughout the rest of the treatment.

It would appear that treatment of such a strenuous nature will result in occasional fatalities. While the percentage of *mortality* is extremely low, of course this fact does not give consolation for those cases in which death has occurred. W. T. Hasler, Jr., and L. Spekter (J. A. M. A. 107:102 (July 11) 1936) reported 4 deaths among 280 patients who had had 430 fever treatments. One of these patients had carcinomatosis, 1 gave history of sun-stroke, 1 was greatly debilitated, but in the fourth case there was no contraindication to fever therapy. In the REVIEWERS' experience there has been but 1 fatality among 555 patients, the causative factor in that case not being determined. F. W. Hartman and R. C. Major (Am. J. Clin. Path. 5:392 (Sept.) 1935) reported 2 fatalities. C. A. Neymann (Proc Roy. Soc. Med. 29:151 (Dec.) 1935) reported 18 fatalities among 742 patients with dementia paralytica treated by electropyræxia in a collected series of cases of more than 25 investigators. In 1932, F. W. Bishop, C. B. Horton and S. L. Warren re-

ported 2 fatalities resulting from the diathermy method of treatment. One of these patients was an alcoholic with cerebrospinal syphilis; the other had chronic encephalitis. One fatality in a case of chronic encephalitis resulting from the use of a nonluminous type of cabinet was reported by J. L. Berris in 1933.

However, sight should not be lost of the great numbers of patients who have been treated without the development of any serious complications. Thus, W. M. Simpson (*loc. cit.*) reported that with the use of the Kettering hypertherm over a 4-year period, 431 patients had 3204 fever treatments with no fatalities; only a few superficial burns were encountered early in the work. The REVIEWERS have given 2174 fever treatments with 1 fatality. On the whole, it might therefore be said that the risk to any one patient is very small indeed.

Of the *pathologic changes*, various hemorrhagic processes have been noted in some cases (hemorrhagic pneumonia has occurred or deterioration and hemorrhage may occur in the suprarenal cortex). Since both fever therapy and sodium amytal (which is frequently used as a sedative in fever therapy) tend to produce marked dilatation and engorgement of the blood vessels, it is suggested by F. W. Hartman and R. C. Major (*loc. cit.*) that the combination should not be used. Tuberculous lesions are more extensive among animals that have been treated with fever artificially than they are among those that have been used as controls (G. R. Duncan and E. S. Mariette). In subacute bacterial endocarditis there is apparently danger that fever therapy will produce multiple emboli according to Freund and Watts.

**Therapeutic Indications.**—As is the case with every new therapeutic agent, fever therapy is being recommended in the treatment of a large number of



diseases, and it has been used in no less than 50 different ones. The results of such treatment in the majority of these cases have not been encouraging, although for a selected few the method has given promise of great usefulness. Space does not permit detailed consideration of the use of artificial fever produced by physical means in the treatment of all the conditions for which it has been recommended, which are as follows: adiposis dolorosa, allergic dermatitis, arteriosclerosis, bacterial endocarditis (subacute), bronchial asthma, bronchiectasis, Buerger's disease, cerebral atrophy (with chronic otitis media), chorea, chronic sinusitis, dermatitis herpetiformis, epidemic encephalitis, epilepsy, "gall-bladder infections," gonorrheal arthritis, gonorrheal corneal ulcer, gonorrheal endocervicitis, gonorrheal epididymitis, gonorrheal prostatitis, gonorrheal salpingitis, gonorrheal urethritis, pelvic inflammatory disease, "hepatic infections," Hodgkin's disease, infectious arthritis, interstitial keratitis, iritis (subacute), meningococcus septicemia, multiple sclerosis, mycosis fungoides, optic atrophy, osteogenic sarcoma, osteomyelitis, Parkinson's syndrome, peripheral vascular disease, psoriasis, psychoses, pyelitis, radiculitis, Raynaud's disease, rheumatic fever, sciatic neuritis, scleroderma, septicemia (staphylococcic), syphilis, syphilitic meningitis, ocular syphilis, syphilis of the nervous system, trichinosis, tuberculosis, tumors, and undulant fever.

The REVIEWERS wish to emphasize most strongly that it is probable that fever therapy is of little or no value in the treatment of a number of the diseases just mentioned, and in some it is distinctly dangerous to attempt fever therapy. Studies in the past year have added greatly to information in the treatment of some diseases.

SUBACUTE BACTERIAL ENDOCARDITIS (Endocarditis Lenta).—Studies by Freund and Watts have demonstrated very definitely that, although there was apparently some slight temporary relief of pain and lowering of temperature following artificial fever therapy, no permanent beneficial effects were noted in any of their cases. Because of the presence of soft vegetations on the endocardium, the very marked increase in blood velocity produced by fever therapy apparently increases the danger of embolism. Either cerebral or other embolism may occur. Freund and Watts have also demonstrated that *Streptococcus viridans* can resist the very highest temperatures that the human body can tolerate. These results constitute a warning to abandon any further attempts to use fever therapy in subacute bacterial endocarditis.

BRONCHIAL ASTHMA.—The findings of Desjardins and Popp, H. W. Hefke, and J. J. Sheldon indicate that of 117 cases, the findings were favorable in 104 cases, unfavorable in 10, and indifferent or slight in 3 cases. These results would indicate that well-equipped departments of fever therapy in hospitals are justified in continuing to administer fever therapy to patients who have intractable bronchial asthma which has failed to respond to all other means of treatment. However, the results are frequently only temporary, and in some instances no improvement will obtain. Because of the severity of the treatment, fever therapy should not be attempted unless all other means have failed. In no instance should fever therapy be attempted as an office procedure. K. Phillips (Arch. Phys. Therapy 17:282 (May) 1936) is of the opinion that hyperpyrexia will be of only temporary, if any, value. When used in conjunction with some other form of treatment he believes that it is a most valuable adjunct.

**CHOREA.**—The recent report of Neymann, Blatt and Osborne (*loc. cit.*) revealed that 25 patients treated by them by means of electropyrrexia responded favorably in every case, *i. e.*, choreiform movements ceased promptly. Included were several cases with an associated rheumatic carditis, which does not contraindicate hyperpyrexia. While the total number of cases is still too small to draw any final conclusions, it would seem that since no untoward effects have been reported, well-equipped institutions would be justified in continuing the use of artificial fever therapy in chorea until such time as more data has been secured.

**GONORRHEAL ARTHRITIS.**—Studies reveal that, with one exception, all investigators reported startlingly good results in the treatment of gonorrheal arthritis with artificial fever by physical means (P. S. Hench: *J. Lab. and Clin. Med.* 21:524 (Feb.) 1936; C. W. Strickler, Jr.; W. M. Simpson: *loc. cit.*; T. B. H. Anderson, R. C. Arnold, and J. A. Trautman; T. G. Schnabel and F. Fetter; P. S. Hench, C. H. Slocumb and W. C. Popp; H. W. Kendell and W. W. Webb. These reports reveal that after treatment with artificial fever, approximately 60 to 80 per cent. of the patients were symptom-free; an additional 10 per cent. were markedly improved, and the other 10 per cent. were unimproved. Results in treating chronic gonorrheal arthritis were less striking. The studies indicate that the earlier in the course of the arthritis the treatment was given, the greater was the opportunity for complete subsidence of the infection and for nearly complete restoration of articular function.

**GONORRHEAL OPHTHALMIA.**—Reports indicate that the use of fever therapy induced by physical means in these cases "causes subsiding of the inflammation and disappearance of the organisms, accelerates healing, and

shortens the stay in the hospital." Uniformly favorable results were reported from the use of artificial fever in these cases (M. H. Metz: *J. A. M. A.* 106:1658 (May 9) 1936; W. T. Hasler, Jr., and Louis Speker: *loc. cit.*)

**OTHER GONORRHEAL COMPLICATIONS.**—Studies of gonorrheal endocervicitis, gonorrheal prostatitis, gonorrheal salpingitis, and gonorrheal pelvic inflammatory disease indicate that if proper technic is used, these complications will respond favorably to prolonged, high artificial fevers. In 187 cases of gonorrhea, 121 patients were clinically "cured" and 28 were improved; in 4 cases results were not reported. These figures are startlingly good (Warren, Carpenter, and Boak; and Desjardins and Popp). There is convincing evidence, according to W. M. Simpson (*loc. cit.*), based on studies of thermal death times of organisms *in vitro* and the clinical response of patients with gonococcic infections to artificial fever therapy that it is possible, in most instances, to destroy gonococci in the various lesions of the disease with sustained high temperatures. Besides this sterilizing effect, there is also evidence that artificial fever therapy stimulates immune reactions. Despite the severity of this type of treatment, its use by properly organized teams of workers in well-equipped institutions seems justified in cases in which no contraindication is present.

**INFECTIOUS ARTHRITIS.**—The work of various investigators shows that about 30 per cent. of the patients with infectious arthritis who were treated with artificial fever were significantly improved; the other 70 per cent. showed little or no improvement (C. L. Short and W. Bauer; Hench, Slocumb and Popp; R. M. Stecher; C. F. Tenney and W. B. Snow; C. W. Strickler, Jr.).

**MENINGOCOCCUS SEPTICEMIA.**—Three "cures" have been reported following the

use of prolonged high fevers, 7 to 10 hours at 106.8° F. (41.5° C.) (E. S. Platon, E. McElmeel, and A. Stoesser: *Minnesota Med.* 19:781 (Dec.) 1936; A. E. Bennett, J. P. Person, and E. E. Simmons: *Arch. Phys. Therapy* 17:743 (Dec.) 1936).

**MULTIPLE SCLEROSIS.**—Several investigators (Desjardins and Popp; A. E. Bennett and B. Austin; and H. W. Hefke) reported the treatment of this condition with induced fever. The results were for the most part unfavorable, although the number of cases reported is too small to permit the drawing of any final conclusions.

**MYCOSIS FUNGOIDES.**—The report of J. Peyri and that of J. V. Klauder (*J. A. M. A.* 106:201 (Jan. 18) 1936) signifies that of 10 cases of mycosis fungoides in which artificial fever produced by physical means was used, moderate improvement, which apparently was temporary, was noted in 8 cases. In 1 case treatment had to be discontinued because of an intercurrent, severe herpes zoster; in the other case treatment was of "no avail."

**PARKINSON'S SYNDROME.**—H. W. Hefke and also J. C. Rogers reported the treatment of this condition with fever therapy; W. H. Schmidt had previously advocated fever therapy for the postencephalitic type of this syndrome. It would probably be best to heed the statement of D. Riesman, *viz.*, that "fever therapy in the form of diathermy or malarial or bacterial injections seems to produce no permanent benefit. It may even do harm."

**SYPHILIS (EARLY).**—Reports indicate that artificial fever therapy combined with chemotherapy affords better results than can be obtained by the use of either alone (C. A. Neymann, T. K. Lawless, and S. L. Osborne: *J. A. M. A.* 107:194 (July 18) 1936; Epstein and Cohen; W. M. Simpson: *loc. cit.*). In the in-

vestigation of the treatment of primary syphilis, as well as the later stages, fever therapy (50 hours of sustained rectal temperatures between 105° and 106° F. (40.6° and 41.1° C.) was combined with 30 injections of an antisyphilitic agent. Cutaneous manifestations of the disease, including chancres, responded with surprising promptness, and no living motile spirochetes were found in any of the primary lesions after the first fever treatment. Progressive improvement in serologic reactions appeared in the majority of cases, and there was no evidence of clinical or serologic relapse. The results of treatment in control groups in which either fever therapy alone or chemotherapy alone was used indicated that either of these methods alone was often inadequate. In the article by Neymann and others, the value of artificial fever therapy in the treatment of syphilis is discussed pertinently.

**OCULAR SYPHILIS.**—Studies indicate that the combined fever-chemotherapy technic of Simpson is of considerable value in the treatment of some forms of ocular syphilis, particularly interstitial keratitis, exudative uveitis, optic neuritis, and neuroretinitis. The greatest field of usefulness of artificial fever and specific therapy may well be their early application to prevent later ocular manifestations.

**SYPHILIS OF NERVOUS SYSTEM.**—Reports vary as to the efficacy of artificial fever induced by physical means in the treatment of dementia paralytica, tabes dorsalis, and other types of syphilis of the central nervous system. Some investigators have secured more favorable results by the use of this means of inducing fever; others have found that malarial inoculation seems to give more favorable results. Simpson (*loc. cit.*) found that of his patients with *dementia paralytica* who were subjected to combined fever and chemotherapy, 77 per

cent. experienced clinical remission and only 4 per cent. showed no improvement. Neymann and Osborne have added to reports of their own favorable results the observations of other workers obtained by application of artificial fever therapy to the treatment of patients with *dementia paralytica*. Of 544 patients in all stages of the disease, 161 (30 per cent.) obtained complete clinical remission, while 155 (29 per cent.) were distinctly improved. Simpson also observed favorable improvement in patients with *tabes dorsalis* treated by fever induced by physical means, and from his experiences was of the opinion that "results obtained in the treatment of symptomatic neurosyphilis, asymptomatic neurosyphilis, ocular syphilis, and resistant sero-positive syphilis are at least comparable, if not superior, to the results obtained with the more hazardous, time-consuming and inconstant malaria therapy."

A. E. Bennett (J. A. M. A. 107: 845 (Sept. 12) 1936) reported favorable results in 14 cases of *tabes dorsalis* in which patients were treated according to the Simpson technic when previous methods had failed. In a preliminary report C. H. Barnacle, F. G. Ebaugh, and J. R. Ewalt (*Ibid.*) 107: 1031 (Sept. 26) 1936) discussed the comparative study of 30 patients with *dementia paralytica* who were treated by combined artificial fever therapy and tryparsamide, as compared with an equal number treated by malaria therapy, both methods being followed by chemotherapy. They found 70 per cent. (21 cases) were definitely improved in the artificial fever series, whereas 63.3 per cent. (19 cases) were definitely improved in the malaria group. Serologic reactions in the cerebrospinal fluid did not parallel the clinical results in either group. R. H. Kuhns, (*loc. cit*) reported the observation of a higher percentage of improvement among

patients treated for dementia paralytica by artificial heat (electric blanket) than in those treated by malarial inoculation.

S. H. Epstein, H. C. Solomon and I. Kopp (J. A. M. A. 106: 1527 (May 2) 1936) reported a review of the literature which showed that of 648 collected cases of dementia paralytica in which patients were treated by diathermy and hyperpyrexia, remissions were reported in 27 per cent., whereas in cases in which treatment was with malaria, similar remissions were observed in 45 per cent.; in cases in which patients were treated with tryparsamide remissions occurred in 42 per cent.

TUBERCULOSIS. — Investigations indicate that artificial fever should be employed with greatest care even in experimental studies (M. H. Metz; J. E. Benjamin; G. R. Duncan and E. S. Mariette; R. C. Major, H. P. Doub and F. W. Hartman). There is great danger of doing harm to the patient if fever therapy is used in this disease, and the study of this phase of treatment of tuberculosis should, for the present, remain entirely in the hands of research groups.

UNDULANT FEVER.—L. E. Prickman and W. C. Poop (Proc. Staff. Meet., Mayo Clin. 11: 506 (Aug. 5) 1936) have noted a rather striking response to fever therapy in 3 cases of undulant fever. The REVIEWER recently treated a fourth patient, who has shown a sudden and very spectacular remission of the chills and fever following 3 sessions of high fever artificially produced. The number of patients is insufficient for one to draw any final conclusions in regard to this disease.

CONCLUSIONS WITH REGARD TO DISEASES TREATED.—The studies that have been made during the past year indicate that the chief sphere of usefulness of fever therapy by physical means lies in the treatment of *gonorrhea*, both

acute and chronic, and of its complications. It would appear that it may be of value in the treatment of *syphilis*, particularly when it is combined with chemotherapy. While there is a suggestion that artificial fever produced by physical means may be helpful in the treatment of intractable *bronchial asthma* and in selected cases of *chronic infectious arthritis*, *chorea*, and *undulant fever*, nevertheless clinical data are not sufficient to permit any final conclusions to be drawn. Its value in about 40 other diseases remains to be proved. It seems to offer promise of considerable usefulness as a therapeutic agent, particularly in the treatment of gonorrhea.

**Conclusion.**—Studies during the past year have emphasized the facts stressed by the Council on Physical Therapy, *viz.*, that production of fever by physical means is strictly a hospital procedure; that it is essential that a well-trained personnel be in complete charge of the work; that skilled nurse-technicians, who have had at least one month's supervised training, administer the treatments; and that a physician be in constant attendance. Patients to be treated by fever should be selected with as much care as are those who are to undergo a major surgical operation.

The dangers that have been mentioned—embolism, hemorrhage, and sudden death—are extremely rare when the administration of the fever is in the hands of a competent, well-organized group.

However, there is certain to be a very slight mortality with a treatment that is as heroic as this. If these treatments are given without proper control or are considered as simple office procedures, there is danger of harm to the patient or even death.

Opinions vary as to the best and safest physical means of producing fever. Almost any one of the methods described in this article may be used with the confidence that it will produce favorable results provided the team of workers who are using it have developed a good technic for the particular method.

It would seem quite apparent that, for the present, the medical profession as a whole should avoid the use of fever therapy unless there is available an institution properly equipped to administer this type of treatment.

The controversy still goes on concerning the effectiveness of fever produced by malarial inoculations or injections of foreign proteins as compared to fever produced by physical means. It would seem from a clinical standpoint that the production of fever by physical means offers certain factors of control and safety that make it appear preferable in some instances to the production of fever by malarial inoculations or by injections of foreign protein. Clinical observations would indicate that in the treatment of disease by these two methods the results obtained are somewhat comparable.

## IONIZATION

By RICHARD KOVACS, M.D.

Renewed interest in the time-honored method of percutaneous introduction of medicinal substances by the galvanic current is largely due to newer clinical and research work demonstrating that vasoactive substances, notably histamine and choline compounds, when introduced by

ionization penetrate the deeper layers of the skin and exert local as well as systemic effects and are clinically useful in a variety of chronic conditions.

**Physics and Mode of Action.**—H. Rutenbeck (Klin. Wchnschr. 14:228 (Feb. 16, 1935) (Nov. 16) 1935) groups

under the term of *electrophoresis* 3 forms of ionic movement: (1) *Iontophoresis* in ionized solutions is the attraction of the positive and negative ions to the pole with the opposite electric charge. (2) *Cataphoresis* is the transport of non-dissociated molecules and colloids, including the solving fluid itself, from the positive pole (anode) to the negative pole (cathode). (3) *Electronosmosis* is the speeding up of the normal endosmotic power of tissues—only high voltage is effective for this. Optimum effect by ionization can be obtained (1) if the solution contains only dissociated pure medicaments (inorganic ions from the metal used for contact will travel faster than organic ones); (2) if the ions are greatly dissociated (do not use concentrated solutions); (3) if sufficient strength of current is employed a sufficient length of time (at 5 MA strength a 1 per cent. solution of choline shows no general effect in one-half hour, while at 15 MA in 5 to 10 minutes a general reaction—perspiration, increased peristalsis—will occur). Generally speaking, more intense penetration occurs from the positive pole. Ions repelled from the positive pole are heavy metals: copper, zinc, magnesium, alkaloïds, morphium, cocaine, histamine, cholin derivatives, aconitine. The negative pole will introduce salicylates, iodides and bromides.

Ionic *penetration*, according to Harpuder (American Congress of Physical Therapy (Sept.) 1936), takes place at least through the rete Malpighii as far as the corium and along the hair follicles and coil glands; such penetration is not obtainable by medicated ointments or solutions. Effects upon deeper or internal tissues can only be expected from drugs acting upon reflex connections between the skin and deep tissues. Ionization (*electrophoresis*) is not suitable for systemic treatment because the

amount of drug introduced into the skin and carried into the circulation cannot be estimated with accuracy. Ionization is essentially an introdermal therapy and its advantage is the possibility of covering large areas and in its slow, prolonged, localized action.

#### ***Apparatus and General Technic.***—

Any form of galvanic current generator will suffice. Simplest and most inexpensive are large "B" batteries (50 volts and 100 amperes) when equipped with a current control (rheostat) and milli-ampere meter. They can be employed in homes where there is no current supply. The average "B" battery will need replacement only about once a year. Galvanic "rectifiers" change the alternating supply current into a direct (galvanic) current through a vacuum or valve tube. Most expensive are motor generators, but they also furnish a variety of "low frequency" currents for muscle and nerve stimulation.

The general *technic* of ionic medication is described by R. Kovács (Physiotherapy Rev. 16:3 (Feb.) 1936). An "active" electrode is made of sufficient thickness of absorptive material and serves to hold the solution; gauze of a thickness of one-half inch (about 16 layers) is best, but cotton or felt of the same thickness may serve also. Soaked with the solution at a temperature of comfortable warmth, the pad is laid on with a good contact over the area to be treated. Upon the pad is placed a metal plate of somewhat smaller size, care being taken that the metal nowhere touches the skin; even a minute contact may lead to a chemical burn.

Special technics have been developed for the introduction of vasodilating drugs. For treatment of mucous surfaces—the cervix, nasal cavity or the inner ear—a metallic electrode, solution or packing containing the ions, is placed in direct contact with the walls of the cavity. A pad electrode of larger size than the active electrode serves as a dispersive electrode in all treatments; it is soaked in hot water or saline solution and placed in good contact with any convenient part. A foot- or arm-bath may also be used as a dispersive electrode. Connection of the active and dis-

persive electrodes to the correct poles is of the utmost importance. If the terminals of the galvanic apparatus are not permanently marked for polarity, it can be quickly determined by placing the cord tips into salt water 1 inch apart and turning on a small amount of current. The cord tip around which a large number of bubbles (hydrogen gas) immediately appear is the negative pole.

**Histamine Ionization.**—Histamine is a vasodilator substance which is formed in the skin as a result of thermal, mechanical, or chemical irritation. After being produced pharmacologically, it was originally employed in the form of injection for rheumatic conditions. D. Deutsch reported first on its administration by ionization. In 250 patients with *muscular rheumatism* and *chronic arthritis* and *sciatica*, which previously resisted all antirheumatic measures, there was permanent improvement or full restitution in the majority of cases. The number of treatments varied from 4 to 20; in acute cases often a single treatment was sufficient.

The technic employed by Deutsch follows:

Moisten blotting paper of a size corresponding to the area to be treated with a 1:1000 solution of histamine acid phosphate; after placement it is covered with a metal foil connected to the positive pole; the dispersive pad is connected to the negative pole. A few milliamperes ( $\frac{1}{2}$  MA per sq. cm.) of current is allowed to flow for 1 or 2 minutes. After removing the electrode, the skin looks reddened, wheals appear and form a patch of urticaria and the temperature of the treated part rises 3° to 5° F. Microscopically, a dilatation of the minute arterioles and capillaries and increased permeability of vessel walls are shown. All this gradually recedes and the skin returns to normal appearance in a few hours.

**Undesirable results** of systemic absorption are: headache, tachycardia, feeling of constriction of the chest and faintness. Deutsch attributes the favorable results to a nervous reflex effect on muscle pain and spasm without an anesthetic effect in the ordinary sense. He

emphasizes that histamine will only relieve pain which is connected with local tenderness or limitation of motion.

J. C. Doane found benefits with histamine ionization in cases in which the basic difficulty was local ischemia due to a vasospasm or to a deficiency in collateral circulation accompanying an obstruction lesion. The relaxation of painful muscle spasm and the production of localized counterirritant action appear also useful. The conditions treated were *arteriosclerotic endarteritis*, *Buerger's disease*, *spasticity in spinal cord disease or injury* and *myalgias*. He employed 1:10,000 solution of histamine hydrochloride in a glass jar into which the extremity to be treated was immersed and 10 MA of current was applied for 5 to 10 minutes from the positive pole. A dispersive pad on the thigh was connected to the negative pole. D. H. Kling (Arch. Phys. Therapy 16:466 (Aug.) 1935), using Deutsch's technic, reports on 150 cases treated with histamine ionization and claims 80 to 100 per cent. cure or improvement in *affections of soft tissues, muscles and bursæ*; 66 per cent. improvement in *posttraumatic arthritis*; 76 per cent. improvement in *rheumatoid arthritis* and 60 per cent. improvement in *osteoarthritis*. According to P. S. Hench and his associates (Ann. Int. Med. 9:883 (Jan.) 1936) these figures do not appear to be checked by controls. F. S. Mackenna (Lancet. 1:364 (Feb. 15) 1936) employed a histamine ointment rubbed in the skin which is previously scarified; a current strength of 100 to 150 MA is used from 3 to 25 minutes, cutting it off as soon as the first sign of a systemic reaction—flushing of the face—appears. Reporting on 2496 treatments, he found best results in *fibrositis*, *neuritis* and *traumatic arthritis*. Individually controlled technic is essential. The average number of applications was 25 and at least 12

were required for any permanent improvement.

**Ionization with Choline Compounds.**—Choline is a vasoactive substance acting as an antagonist to atropine; it stimulates the parasympathetic nerves and dilates the peripheral vascular system. Among several choline compounds suitable for ionic introduction, most extensive work was done with mecholyl (acetyl-bitamethyl choline chloride). J. Kovács, L. L. Saylor and I. S. Wright (Am. Heart. J. 11:

the fact that defective peripheral circulation and disturbed blood supply to the affected joints are apparent in many cases of chronic arthritis. In *peripheral vascular disease*, where organic occlusion has been the major factor, the choline compounds have not been of marked value, while in vascular disease in which spasm is the major factor, the use of the choline compounds proved helpful. Strikingly good results were seen in *Raynaud's disease*; in 10 patients treated there was an increase of comfort and

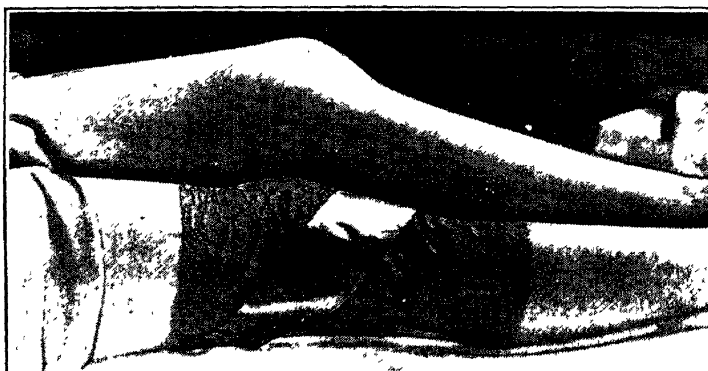


Fig. 1—Technic of mecholyl ionization. (R. Kovács: "Electrotherapy and Light Therapy," Lea and Febiger, Phila., 1935.)

53 (Jan.) 1936) summarize 2 years' experience with choline ionization. One hundred and seventeen cases of *chronic arthritis* were treated from 2 weeks to 2 years with an average of 2 treatments per week; of 44 *osteoarthritics*, 31 reported definite improvement; while out of 73 with *rheumatoid arthritis*, 50 claimed improvement; in both groups certain individuals responded remarkably, but there were frequently observed arthritis patients with sudden remissions, regardless of the therapy used at the time. The authors consider mecholyl ionization a palliative treatment, useful in chronic arthritis, especially of the rheumatoid type, where other methods of physical therapy directed at the relief of local conditions frequently fail. The rationale of treatment is based on

a decrease of the frequency and severity of attacks; in 4 of these patients painful ulcerations healed completely. Complicating *scleroderma* also improved definitely. O. Abel, Jr. (J. Missouri M. A. 32: 351 (Sept.) 1935) reports 90 per cent. relief in 51 cases of *chronic osteoarthritis* and *rheumatoid arthritis*, but has no data on prolonged observation of these cases.

L. Martin (American Congress Physical Therapy (Sept.) 1935) reports that of 83 arthritic patients treated, 55 per cent. with *infectious arthritis* were benefited; some became symptom-free. Seventy-nine per cent. with *metabolic forms of arthritis* were helped; some became symptom-free. Patients with severe chronic generalized infectious arthritis derived only temporary palliative benefit.



In the group of *hypertrophic arthritis*, where constipation was a factor, relief of both was obtained in 79 per cent.

In the *technic* of mecholyt ionization, J. Kovács (Am. J. M. Sc. 188:32 (July) 1934) employs a  $\frac{1}{2}$  per cent. solution for saturating reinforced asbestos paper and wrapping this around the affected joints (Fig. 1). A fairly large malleable metal plate is placed on the moist paper and connected to the positive pole of a galvanic generator and a very large dispersive moist pad is applied to the back and connected to the negative pole (Fig. 2) The

increase of pulse rate and peristalsis, likewise reduction of blood-pressure. These can be immediately checked by subcutaneous injection of  $\frac{1}{100}$  grain (0.6 mg.) of **atropine**. A. J. Kotkis and R. H. Melchionna (Arch. Psys. Therapy 16:528 (Sept.) 1935) confirmed these physiologic effects.

In the treatment of *varicose ulcers*, J. Kovács (American Congress of Physical Therapy (Sept.) 1936) re-

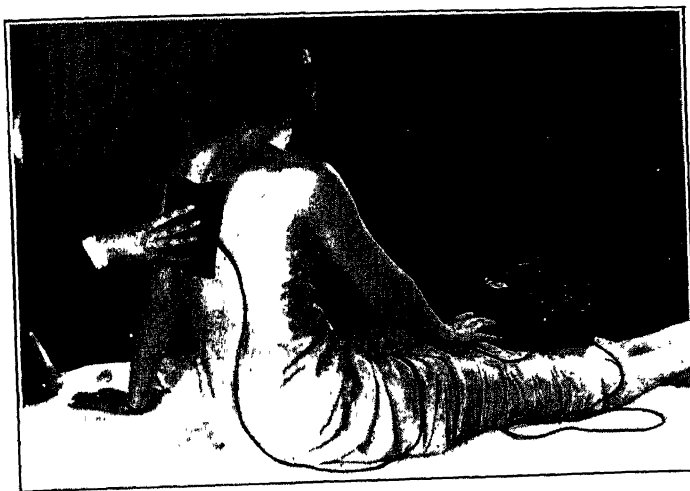


Fig. 2.—Technic of mecholyt ionization. (R. Kovács: "Electrotherapy and Light Therapy," Lea and Febiger, Phila., 1935.)

current is slowly increased from 5 to 20 or 30 MA and kept up for 20 minutes. After treatment, the part is dried and kept covered.

The characteristic local reaction during treatment is a feeling of prickling followed by warmth. Immediately after treatment "gooseflesh" appears accompanied by local hyperemia and perspiration of the treated skin area. The latter may continue from 6 to 8 hours. The surface temperature of the area under treatment first rises then drops under profuse perspiration (with accompanying evaporation), and finally rises above its former level in from  $\frac{1}{2}$  to 5 hours. General effects are observed when large areas were treated, or there is a special sensitivity of the patient; they consist of flushing, general sweating, salivation,

ported on 43 cases in which mecholyt ionization was completed; with the exception of 2 patients, the ulcers healed in all cases. The patients were unselected and careful experimental conditions were maintained. With 3 exceptions, patients had been through a control period ranging from 1 to 37 years, during which time all recognized forms of treatment had been tried; during the period of treatment no patients were hospitalized or put to bed, but were urged to continue their daily occupations; no other forms of treatments, such as injections, were used during the course of the ionization. A plain petrolatum dressing was permitted during the course of the early stages of the treatment if it made the patient more comfortable. Veins, if in-

dicated, were injected only after the ulcer had healed.

The technic of treatment consisted in wrapping around the foot and leg reinforced asbestos paper saturated with  $\frac{1}{2}$  per cent. solution of mecholyl and connecting this to the positive pole. A dispersive pad is connected by the negative pole. The ulcerated area is not

local diaphoresis continuing from 4 to 8 hours after the treatment, which may reduce the edema resulting from hydrostatic pressure, the relief of the tissues of this overload of fluid may permit healing.

**Summary.**—*Histamine ionization* by the generally used technic produces an intense local "counterirritant" effect and

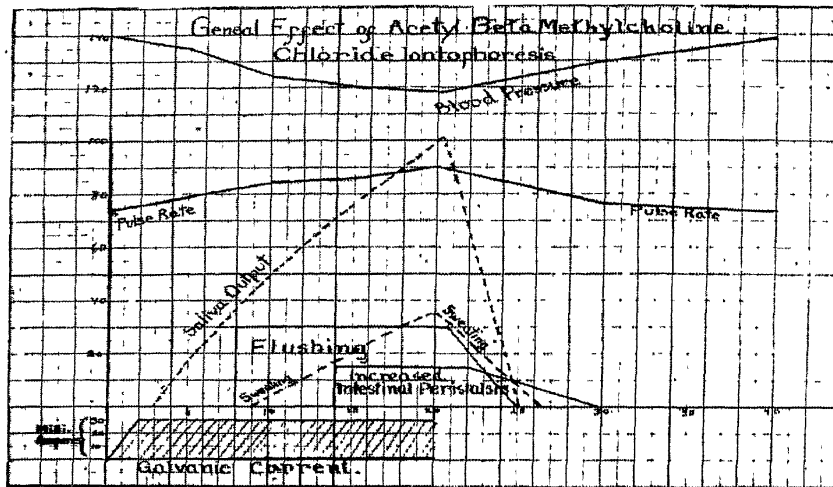


Fig. 3.—Curves showing systemic effects of mecholyl ionization. (R. Kovács: "Electrotherapy and Light Therapy," Lea and Febiger, Phila., 1935.)

covered during treatment until a firm scab has formed over it. The current used is 20-30 ma., applied from 20 to 30 minutes, and treatment is generally given 2 or 3 times weekly.

L. Saylor, J. Kovács, A. W. Duryee and I. Wright (J. A. M. A. 107:114 (July 11 1936) explain the mechanism of healing of ulcers by mecholyl ionization partly by increased local circulation, resulting in a more rapid removal of the waste products and improved local nutrition, thus producing regeneration of the tissues, and partly by the marked

is applied in a very dilute solution for a few minutes only. Systemic effects are an exception. It is reported to give best clinical results in *muscular affections*. *Mecholyl ionization* produces a less intense local reaction, its effect amounting to a deposition of the drug in the deeper layers of the skin and its gradual absorption. It is applied in a more concentrate solution and for a longer period of time. Systemic effects occur as a rule. It is reported to give best results in *joint affections* and also in *varicose ulcers*.

## PASSIVE VASCULAR EXERCISES (TREATMENT BY ALTERNATING SUCTION AND PRESSURE)

By GESA DE TAKATS, M.D.

A physical method of dilating collateral arterial pathways of an extremity, whose major arterial pathways had been occluded by trauma or disease, has been designated as passive vascular exercise. While the idea of releasing the existing atmospheric pressure of about 15 pounds per square inch of surface and thus dilating the small vessels either by continuous or alternating suction was proposed many years ago, L. G. Herrmann ("Passive Vascular Exercises," J. B. Lippincott and Co., Phila., 1936), of Cincinnati, and E. M. Landis and L. H. Hitzrot (Am. J. M. Sc. 189:305 (Mar.) 1935), of Philadelphia, have in recent years aroused great interest in this problem by constructing efficient mechanical devices and outlining the indications and results of this form of physical therapy.

**Physiologic Considerations.**—When a major or a middle-sized artery is blocked, nature's method to develop collateral circulation around the obstruction is to raise the blood-pressure above the obstruction and diminish peripheral resistance below it. The collateral channels, which carry the side-tracked blood, are preëxistent, but their diameter is small, as they are not accustomed to carrying much of a load. The fate of the limb whose major or medium-sized arterial pathways are occluded, will depend to a large extent on the site of obstruction, on the number and size of the available collaterals, on the vasomotor tone of the peripheral vascular bed, and on cardiac reserve. Every one of these factors may contribute to death, recovery or subsistence of the affected part.

Passive vascular exercises cannot influence the action of the heart, nor can

they change the site or extent of the vascular occlusion. They may stretch the smaller vessels and collaterals if they are unaffected by disease and they may influence vasomotor tone. Thus, it has been pointed out by M. R. Reid and L. G. Herrmann (Ann. Surg. 102:321 (Sept.) 1935) that the dramatic action of suction and pressure in case of peripheral arterial embolism must be based on the release of vessel spasm. Further evidence for this mechanism is supplied by the beneficial effect of papaverine in cases of acute vascular occlusion (G. de Takats: J. A. M. A. 106:1003 (Mar. 21) 1936). For the release of this vasomotor tonus during treatment by suction and pressure, Landis has advocated the use of heat from the start; later, Herrman and, recently, F. V. Theis and M. R. Freeland (*Ibid.* 107:1097 (Oct. 3) 1936) have emphasized the advantage of combining heat with passive vascular exercise. The method and extent of applying heat will be discussed later.

When the terminal vascular bed is closed or destroyed, no dilatation of collaterals can improve the oxygenation of tissues. In such cases of "arteriolar destruction," this therapy is of no avail or may even increase stasis and accelerate necrosis.

To explain the beneficial effects of passive vascular exercises on peripheral vascular disease, it has been generally assumed that actually more blood is being sucked into the extremity encased in an air-tight boot. The objective changes produced are the restoration of a normal pink or even red color to the toes, the rise in skin-temperature, the increased moisture, and a mobility of

the joints (Herrmann: *loc. cit.*). The capillary microscope reveals a filling and stretching of the capillaries. It has been generally overlooked that such changes can readily be brought about by the venous congestion produced by the cuff-pressure during the phase of suction and that feeling of warmth, which patients experience, does not occur during the phase of suction, but during the phase of positive pressure. For this reason, at least part of the beneficial effects of alternating suction and pressure therapy are dependent on the production of an intermittent venous hyperemia (W. S. Collens and N. D. Wilensky: *Am. Heart J.* 11:705 (June) 1936; G. de Takats, F. K. Hick and J. S. Coulter: *In Press*); during venous congestion the minute vessels are filled and stretched to capacity and during release the reactive hyperemia attracts fresh blood. There still remains, of course, the effect of decreased environmental pressure on the cutaneous vessels, but whether this subatmospheric pressure exerts any influence on the deeper vessels is a matter of conjecture.

Another explanation of beneficial effects of alternating suction and pressure has been attempted by Theis (*loc. cit.*). Because of the fall of the oxygen-saturation of the venous blood in the saphenous vein and the rise in skin-temperatures after treatment, he believes that an increase in tissue-metabolism takes place and this, and not an improvement in circulation, is responsible for the beneficial effects. The fall in venous oxygen, however, can equally be explained by the venous stasis, as mentioned above; the rise in temperature can readily be produced in any air-tight boot but without any suction and pressure. It has furthermore been shown by Landis that the compression and thinning of the air encased in the boot may in itself give in to an increase in temperature.

**Methods of Application.**— There are various types of apparatus on the market, but fundamentally they employ the following principle:

The treated extremity is encased in a transparent boot, made of glass or of cellulose acetate, through which the color-changes of the extremity may be observed. A pressure-dial on the boot serves to register the amount of suction or pressure obtained. The boot is then fastened to the extremity, usually at mid-thigh, with the help of rigid or soft rubber cuffs, which are supplied in several sizes to fit the thigh. Obviously they should not be too tight, and yet must prevent leakage, if the desired pressure-changes are to be obtained. By the use of double cuffs or cuffs with flaps, this problem has been fairly well solved. The extremity is elevated from 10 to 12 inches above the heart. The boot or boots, as many as four at a time, are connected to a suction-pump, which is preferably portable, noiseless, and which can be adjusted to different pressures and ratios between positive and negative pressure.

Most machines now are using the cycles described by Landis, *viz.*, a negative pressure from 80 to 120 mm. of mercury for 20 seconds and a positive pressure of 20 to 40 mm. for 5 seconds, the changes taking place rather rapidly. Herrmann, on the other hand, uses pressures from  $-80$  to  $+20$  mm. of mercury, the alternation taking place slowly, taking about 2 to 4 cycles a minute; with the 15 second cycle, about 9 seconds are taken for the negative and to 6 seconds for the positive cycle. That the exact timing will slightly depend on the number of extremities treated and the air space in the boots is evident. Both authors have emphasized that in cases of gangrene, impending gangrene or marked capillary stasis, the negative pressures should not exceed 40 mm. of mercury, as more than that may produce pain or accelerate necrosis.

The treatments are given according to the severity of the vascular occlusion and the imminence of gangrene. They can be given for 12 hours a day, 1 hour on and 1 hour off, and they can be given during the night with suitable sedatives. Five hours a day for 2 weeks, a total of 70 hours, should serve as an adequate test, whether or not, the treatment is going to be of any benefit. Although, generally speaking, patients with low blood-pressures and with marked arteriolar involvement give the least response, no satisfactory

method of predicting the benefit to be derived has been found except that of an intensive treatment for trial. Even in cases in which peripheral vascular disease has advanced to a point where there is no increase in circulation after the abolition of vasoconstrictor tone, Landis has found it possible to increase the bloodflow by this method.

**Indications.**—Of all the disturbances of peripheral circulation, *acute arterial occlusions* have been most dramatically influenced by this form of therapy. M. R. Reid and L. G. Herrmann (*loc. cit.*) and J. H. Conway (J. A. M. A. 106:1153 (Apr. 4) 1936) have reported outstanding success in this type of lesion. It must be remembered, however, that the concomitant vessel-spasm can be relieved by heat and vasodilators and that the recovery of the limb also depends to a great extent on the site and extent of obstruction (G. de Takats: Am. J. Surg. 33:60 (July) 1936).

Excellent results have been reported on the treatment of *frost-bites*. In a stage of vasomotor paralysis and stagnation of blood in the venocapillary bed, suction and pressure is indicated and useful. More pressure and less suction is to be employed. When thrombosis has taken place, obliterating the terminal vascular bed, or if frank gangrene has set in, the treatment is useless and only delays the removal of tissue which is irrevocably lost.

Of the chronic arterial occlusions of the extremities, *Buerger's disease* has been reported to have given favorable response to this form of therapy by Herrmann (*loc. cit.*), Landis (*loc. cit.*), and Theis (*loc. cit.*). The writer (G. de Takats: J. A. M. A. 103:1920 (Dec. 22) 1934), E. V. Allan and G. F. Brown (*Ibid.* 105:2029 (Dec. 21) 1935), H. Wilson and N. W. Roome (*Ibid.* 106:1885 (May 30) 1936), and J. H. Conway (*loc. cit.*) did not find any decided benefit in this group of patients. Allen and Brown stated that the

results with the intravenous injection of typhoid vaccine are so good that this type of treatment cannot be compared with it. In the acute inflammatory stage and in the late stages of arteriolar destruction, suction and pressure treatments cannot do any good and may even be harmful. One of the greatest obstacles to the successful treatment of Buerger's disease is the unusually high vasomotor tone, which is maintained reflexly from the diseased segments of the vessels. Recent observations on the treatment of sympathectomized patients by alternating suction and pressure indicate that the removal of vasomotor influence definitely improves the effect of this treatment on Buerger's disease.

By far, the overwhelming majority of patients suffering from peripheral vascular disease suffer from *arteriosclerosis with or without diabetes*. It is this group of patients that needs a real improvement in previous forms of therapy. While Allen and Brown (*loc. cit.*) and Wilson and Roome (*loc. cit.*) do not feel that decided benefit of any kind has been obtained, most authors report a definite improvement, which is permanent enough so that a balance between arterial occlusion and efficient collateral circulation has taken place.

The difficulty in evaluating the merits of this treatment lies in the fact that such patients are also treated by: (1) rest in bed, (2) mild heat, (3) plenty of fluids, (4) abstinence from tobacco and (5) vasodilators. (G. Herrmann and L. Herrmann: Texas State J. Med. 32:340 (May) 1936.) In addition, the hospitalization of these patients enables the physician to regulate the patient's diet and to establish surgical care of the wounds, ulcerations or necrosis. There is, finally, a psychic influence, which by no means should be disregarded. These patients are in fear of losing part of their extremity; they have tried other

measures which have failed; their hope is in this mechanical device, which will restore the circulation to normal. It must also be taken into consideration that many of the elderly arteriosclerotics have cerebral vascular disturbances; they are easily impressionable, and are delighted or become desperate at the slightest change in their physical condition. Nevertheless, from an experience with a considerable number of ambulatory patients, who have received no medication, no mental suggestions, no diets and whose only treatment consisted of 1-hour treatments by alternating suction and pressure 3 times a week, the writer has gained the impression that, roughly, one-half of them have had subjective relief. A purely objective method of measuring intermittent claudication has recently been developed by L. H. Hitzrot, M. Naide and E. M. Landis (*Am. Heart J.* 11:513 (May) 1936), but has, so far, not obtained wide clinical application.

A number of *indolent ulcers*, *pressure sores* and *perforating ulcers*, which heal slowly because of insufficient circulation or lack of adequate sensory stimuli, are favorably influenced by this method. The reactive hyperemia develops also in anesthetic areas.

**Contraindications.**—From the foregoing it must be obvious that acute or subacute infectious processes, venous and lymphatic obstruction, and obliteration of arteriolar or capillary vessels constitute the most important contraindications.

This treatment is a form of powerful massage and may stir up infection, mobilize clots or rupture blood vessels. The appearance of pain during treatment invariably means that the suction is too intense, the treatment too long, or that the treatment is not advisable. The presence of frank, dry gangrene is not an absolute contraindication, but at the slightest suspicion of a spreading infection or a moist gangrene, treatment should immediately be terminated. Whether a spontaneous demarcation and an auto-amputation of a digit can be expected under this form of therapy has not been conclusively shown.

Lymphedema is seriously aggravated, especially if it is of the peripheral type, owing to a latent and recurring lymphangitis. Thrombophlebitic edema has been seen to flare up during such treatment.

**Conclusions.**—Only 3 years have elapsed since the first publication on this method of treatment. Much of the initial enthusiasm has given way to a sober evaluation of results. It must be clear that any local form of therapy cannot influence the progress of a systemic, cardiovascular disease. If it is able, however, to establish and maintain a collateral circulation in a number of patients to whom nothing could be offered in the past, it will become in its present or more simplified form a valuable adjunct of physical therapy.

## ULTRAVIOLET RADIATION

By JOHN S. COULTER, M.D.

**Fluorescent Effects.**—In dermatologic practice the important fluorescent effects noted when the filtered ultraviolet rays are used as a sole source of light may help to detect pathologic conditions

and to differentiate fungi in cultures. G. M. Lewis and M. E. Hopper (*Arch. Dermt. and Syph.* 34:681 (Oct.) 1936) state that in cases of *tinea capitis* the value of the rays cannot be overstressed,

not only in establishing a *diagnosis*, but as an aid in following the progress of the disease and of determining when cure has taken place. Furthermore, in certain infections with *Microsporon audouinii* when regrowth of hair is considerable, the diagnosis of tinea capitis may be suspected. In such instances, when only scaling of the scalp may be noted, fluorescence of the affected hairs is characteristic. In all types of infections due to *Microsporon* the affected hairs appear as luminous short yellowish green "stubs." In infections with *Trichophyton endothrix* the affected hairs are dull and bluish. In infections with *A. schoenleinii* the color is greenish but less luminous than in the infections with the *Microsporon*.

Animal carriers (particularly kittens) of certain pathogenic fungi may be detected by fluorescence of affected hairs which, when observed under filtered ultraviolet rays, have an appearance identical with that of human hairs affected with the disease.

*Tinea versicolor* and *erythrasmus* show individualistic colors sufficient not only to establish the correct diagnosis, but to determine the extent of the eruption even when it has faded so that its presence cannot be clinically detected: Keratin fluoresces, and when it is increased, more luminosity may be seen. *Warts* and *keratoses* show a bright fluorescence, while *molluscum bodies* exhibit a dark center. Some fading and indistinct eruptions become clearer when observed under filtered ultraviolet rays. Many inorganic substances fluoresce. When a drug such as salicylic acid or a product such as petrolatum is present on skin examined under filtered ultraviolet rays, the underlying condition may be masked.

The type and thickness of the *glass filter* through which the ultraviolet rays pass are of great importance. Divergent results may be obtained by different ob-

servers owing to a difference in the type of glass filter or in its thickness. The authors have found that the wave lengths in the near portion of the ultraviolet part of the spectrum (in the region of 3650 angstrom units) offer optimum fluorescent value. The Corning glass violet ultra No. 586, polished to a thickness of between 4 and 5 mm., is adequate for use. In its molded form it is usually from 7 to 8 mm. in thickness, and unless the source of light is extremely powerful, not enough ultraviolet rays are transmitted to produce the desired results.

The room in which the examination is made must be darkened, and in addition most of the visible rays from the ultraviolet lamp must be excluded by a suitable attachment.

The authors' unit is light, easily attached and detached, and readily stored. Any of the better makes of lamp for the production of ultraviolet rays may be used as a source of light. The material needed for the construction of the attachment is 1 square yard of light-proof black rubberized focusing cloth (obtainable at a camera shop). A hole 5 inches (12.5 cm.) square, or smaller, is cut near the center of the cloth. The edges of the hole are hemmed. The glass filter is then placed over this hole, overlapping the cloth on each side. Elastic loops are sewed diagonally across the four corners to hold the glass in place. If the fit is snug, no light will seep around the edge of the cloth. The cloth is then held up to and placed around the hood of an ultraviolet lamp, and the elastic draw string is tightened until the fit is close enough to exclude visible rays. The approximate cost of the attachment (with 6½-inch 15.51 cm.) square filter is \$5.50.

**Counterirritation by Ultraviolet Light.**—The ultraviolet rays that cause

erythema of the skin may be successfully employed for counterirritation, according to A. Eidinow (Lancet 1:1404 (June 20) 1936). Wavelengths shorter than 3000 Angstrom units applied to the normal white skin cause erythema. The dosage and technic of irradiation controls the degree of skin reaction that results. This can be varied so as to cause a mild erythema or a definite or severe blistering of the skin. Ultraviolet irradiation, therefore, is excellent for counterirritation. The degree of reaction can be accurately defined and controlled. With the chemical and other counterirritants, this is not always possible.

Skin erythema appears about 4 hours after ultraviolet irradiation; a maximum reaction results about 48 hours later and with intensive dosage this erythema may persist for 3 or even up to 12 days.

Eidinow states that the area of skin selected for ultraviolet irradiation is mapped out carefully with a dermatograph pencil. The surrounding skin area is protected from the rays of the lamp by a covering. Usually a skin area measuring roughly 12 by 10 inches is exposed. This irradiated skin area and the surrounding skin margin extending for 1 to 2 inches is immediately covered by overlapping strips of adhesive plaster 2 to 2½ inches in width. The patient

is instructed to leave the plaster undisturbed for 14 days.

Some patients complain of discomfort during the second or third day, while in others, itching of the skin has been observed on the seventh to ninth day. Usually these symptoms are of no serious consequence.

The types of cases selected for treatment by this technic of intensive ultraviolet irradiation were those in which symptoms of acute pain were present (*brachial* and *sciatic neuritis*, *lumbago*, *fibrositis*, etc.); those in whom there was *swelling of joints due to effusion fluid*; those with symptoms of *asthma*, with *dyspnea*, and a definite history of frequent attacks of troublesome respiration.

**ULTRAVIOLET RADIATION IN ERYSIPELAS.**—Lavender and Goldman conclude that ultraviolet radiation is the therapy to be preferred in *erysipelas*. Desmaison (Crón. méd. Lima 53:249 (July) 1936) irradiates not only the involved area, but the surrounding zone of apparently normal skin as well, daily or every other day, using a mercury quartz lamp, distance 50 cm., for 5 minutes for the first and 10 minutes for the following irradiations. He believes pulmonary tuberculosis, myocarditis, heart diseases in decompensation and certain dermatitis of the vesiculous type are *contraindications* of the treatment.



# DIETOTHERAPY

By SISTER MAUDE BEHRMAN, B.S., and MIRIAM ADAMS, B.S.

**INTRODUCTION.**—A review of the important recent work in dietotherapy includes the following: Under the subject of *allergy* the most common food offenders against health are wheat, milk, eggs, chocolate, cabbage, tomatoes and oranges. The subject is a large one and many conditions such as hay fever, asthma, skin conditions, and gastrointestinal upsets, are due to allergy. Allergy as a cause of mucus colitis is now coming to the front.

In *arthritis* Bauer advocates a high vitamin and high caloric diet unless the patient is overweight. Scull and Pemberton suggest dehydrating diets, with adequate calories, high in protein, low in fluid, and high in fat.

A low caloric diet of 750 to 850 calories containing 80 grams of carbohydrate, 50 grams of protein and 30 grams of fat, with adequate vitamin content, is suggested for a bed patient with *coronary thrombosis*. Minerals must also be adequate and the fluid intake limited to 1000 or 1200 c.c. with salt restriction. The basal metabolic rate is lowered while the patient is on this diet and the work of the heart lessened and is thereby given an opportunity to heal and to form collateral circulation.

Low fat, high carbohydrate diets are suggested to replace the high fat, low carbohydrate diet formerly given to patients with *gout*.

Diets low in calcium and high in phosphorus, with the addition of ammonium chloride or phosphoric acid, were found to be the means of causing an increase in the excretion of lead in individuals suffering from *lead poisoning*.

One quart of milk, 180 grams of lean meat and large amounts of turnips, tomatoes, and green peas are suggested as valuable aids to supplement the diet for *pellagra*.

After a case has been diagnosed as *urinary calculi*, the type of stone should be determined and the diet planned accordingly. The following summarizes the types of diets for various types of stone. These diets should all be high in vitamin A.

Uratic calculi—low purine diet and alkaline ash diet.

Calcium oxalate calculi—low oxalate dietary and acid ash diet.

Calcium and ammonium magnesium carbonate and phosphate calculi—low phosphate dietary, acid ash diet.

Systine calculi—alkaline ash diet.

The low caloric ketogenic diet is suggested for *urinary infections* since the original ketogenic diets are too difficult for the out-patient to follow.

**ALLERGY.**—The time has come when it is necessary for the surgeon to investigate his cases to determine whether or not surgical intervention is necessary or whether the case is one of allergy. M. T. Davidson (South. M. J. 29:202 (Feb.) 1936) reports a study made of 200 cases of allergic manifestations in which 8 per cent. reacted to foods alone. The author states that milk was the most common offender of all allergenes and the next common to all was grains of cereals. Among fruits, the peach was the only one which gave much trouble. Bananas and pears did not react in a single one of his cases. To obtain the best results when making

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tests to determine whether an individual is allergic or not, all foods related to any food which causes distress should also be eliminated. For example, where a patient is allergic to milk, then cream and butter and cheese or any food cooked with these foods may have to be omitted. Cases of gastric pain, mucous colitis and other intestinal upsets have been known to respond to treatment after an offending food has been omitted.

Allergy may be a difficult condition to discover. C. H. Eyermann (J. Am. Dietet. A. 12:1 (May) 1936) states that it is not always necessary for a person to eat a food to which he is allergic to receive a reaction, but in some cases may merely need to inhale the food. An example is given of a patient sensitive to the egg, who may receive the same reaction from beating egg whites as from eating the egg. Another patient received allergic symptoms from the odor of frying fish as well as from eating the fish.

The skin tests are not always accurate. Many times a patient will not receive the same reaction from the skin test as he does from eating the food. After all the *trial diet* is the best method of deciding. Foods biologically related must constantly be guarded against. The whole family of legumes may cause distress. The trial diet should first consist of biologically unrelated foods which do not often give allergic reactions. The trial diets are only used over a short period of time, so that the matter of vitamin or mineral deficiencies need give no concern. Should this be important the vitamin concentrate should be considered, whether it does or does not contain anything to which the patient may be allergic.

During the trial period of diets, the patient should become comfortable, and then one new food at a time should be added. In some cases, or in most cases, one new food can be added to each meal for 3 days. If there are no allergic symptoms, the food becomes a permanent part of the diet.

Cooking may effect the reaction which various foods may have. Raw eggs may cause distress, when hard cooked eggs will not. Patients who are allergic to wheat can sometimes eat melba toast. Raw fruits and vegetables more often cause symptoms than do those cooked or canned. Sometimes a food may only cause distress when taken for a series of days. Therefore it is necessary that every patient be studied as an individual and the diet prescribed accordingly.

Notebooks kept by the patients to record food intake and reactions, noting the time of reaction in relation to time food was eaten, are of assistance to any physician when dealing with an allergy case.

Hughes (J. Am. Dietet. A. 12:314 (Nov.) 1936) discusses foods which disagree with healthy people and states that it is difficult sometimes to determine whether or not a person is allergic to a certain food or simply has an idiosyncrasy or dislike for it.

Putting aside all dislikes and idiosyncrasies, he considers that from the viewpoint of both medicine and nutrition, it should be known what foods are most likely to cause indigestion, pain, or more serious reactions in otherwise healthy people.

An investigation of 1000 cases of healthy adults for the purpose of ascertaining what foods disagree most with well people, showed the following results. See Tables I and II.

TABLE I

*Showing Specific Foods Which Disagree With Healthy Young Women and the Percentages of Cases Affected*

The Chief Reactions Are Cited in Order of Their Frequency of Occurrence

| Food                                | Percentage of Cases | Chief Reactions in Order of Frequency                                 |
|-------------------------------------|---------------------|---|
| Onions (raw).....                   | 24.5                | Belching, nausea, headache, distention, regurgitation, vomiting, pain |
| Radishes.....                       | 17.3                | Belching, nausea  |
| Cabbage (cooked).....               | 14.7                | Belching, distention, pain, nausea, regurgitation, vomiting, headache |
| Beans.....                          | 12.4                | Distention, pain, belching, headache, nausea, vomiting                |
| Cucumbers.....                      | 9.5                 | Belching, distention, nausea  |
| Onions (cooked).....                | 9.2                 | Belching, distention, regurgitation, nausea, pain                     |
| Tomatoes (raw).....                 | 6.6                 | Urticaria, canker sores, distention                                   |
| Greasy or fried food.....           | 6.3                 | Pain, urticaria, nausea, distention, burning sensation                |
| Frankfurters.....                   | 6.3                 | Belching, nausea, pain, urticaria, distention                         |
| Bananas.....                        | 6.0                 | Nausea, distention, belching, pain                                    |
| Strawberries.....                   | 5.4                 | Urticaria   |
| Eggs.....                           | 5.2                 | Nausea, urticaria, belching, regurgitation, distention                |
| Chocolate.....                      | 4.9                 | Urticaria, nausea, constipation, headache                             |
| Sauerkraut.....                     | 4.3                 | Belching, pain, nausea, distention                                    |
| Apples (raw).....                   | 4.0                 | Belching, pain, constipation  |
| Nuts.....                           | 4.0                 | Distention, urticaria, pain, belching, headache, sneezing             |
| Cabbage (raw).....                  | 3.7                 | Belching, distention, pain  |
| Tomatoes (cooked).....              | 3.7                 | Urticaria, canker sores, belching, vomiting                           |
| "Meats".....                        | 3.4                 | Distention, nausea, urticaria   |
| Cheese.....                         | 3.4                 | Constipation, nausea, distention, pain, urticaria                     |
| Green peppers (raw).....            | 3.1                 | Belching  |
| "Sweets".....                       | 2.0                 | Urticaria, nausea   |
| Citrus fruits.....                  | 1.9                 | Urticaria, distention, vomiting                                       |
| White bread and flour products..... | 1.9                 | Urticaria, distention, nausea   |
| Sea foods.....                      | 1.7                 | Urticaria, nausea, headache, belching                                 |
| Milk.....                           | 1.7                 | Nausea, pain, vomiting, urticaria                                     |
| Turnips.....                        | 1.7                 | Belching, nausea, pain  |
| Liver.....                          | 1.7                 | Nausea, vomiting  |
| Green peppers (cooked).....         | 1.4                 | Belching  |
| Corn.....                           | 1.4                 | Diarrhea, nausea  |
| Peaches (excess).....               | 1.4                 | Urticaria   |
| Pork.....                           | 1.4                 | Pain, headache, nausea, distention                                    |
| Cauliflower.....                    | 1.1                 | Distention, vomiting  |
| Spinach.....                        | 1.1                 | Nausea, vomiting  |
| Mayonnaise.....                     | 1.1                 | Urticaria, headache   |
| Fish.....                           | 1.1                 | Urticaria, nausea, headache   |

60\* other foods, less than 1% affected

TABLE II

*Showing Specific Foods Which Disagree With Healthy Men and Women (Age Range 30 to 65 Years) and the Percentages of Cases Affected*

The Chief Reactions Are Cited in Order of Their Frequency of Occurrence

| Food                        | Per-centage of Cases | Chief Reactions in Order of Frequency                                     |
|-----------------------------|----------------------|---|
| Onions (raw) . . . . .      | 21.0                 | Belching, nausea, pain, distention  |
| Cabbage (cooked) . . . . .  | 16.4                 | Belching, nausea, pain, headache, distention                              |
| Beans . . . . .             | 15.6                 | Belching, distention, headache, nausea                                    |
| Greasy foods . . . . .      | 11.6                 | Belching, pain, nausea, distention, urticaria                             |
| Cucumbers . . . . .         | 6.8                  | Belching, pain, other miscellaneous symptoms                              |
| Peppers (raw) . . . . .     | 6.0                  | Belching, regurgitation, distention, nausea, pain                         |
| Sauerkraut . . . . .        | 5.6                  | Belching, nausea, distention, pain, headache                              |
| "Sweets" . . . . .          | 4.0                  | Constipation, headache, pain, belching, nausea                            |
| Pork . . . . .              | 4.0                  | Nausea, vomiting, pain, distention, other miscellaneous symptoms          |
| Chocolate . . . . .         | 3.6                  | Headache, urticaria, nausea, pain   |
| Milk . . . . .              | 3.6                  | Pain, vomiting, belching, urticaria                                       |
| Tomatoes (cooked) . . . . . | 3.6                  | Belching, nausea, pain, distention, regurgitation, sour stomach, headache |
| Onions (cooked) . . . . .   | 3.0                  | Belching, nausea, pain, distention  |
| Bananas . . . . .           | 3.0                  | Belching, nausea, pain  |
| Radishes . . . . .          | 2.8                  | Belching  |
| Sea foods . . . . .         | 2.8                  | Nausea, pain, distention, belching, vomiting                              |
| Pineapple . . . . .         | 2.8                  | Pain, headache, distention, nausea, urticaria                             |
| Pastries . . . . .          | 2.8                  | Pain, nausea, vomiting  |
| Starches . . . . .          | 2.8                  | Pain, distention, other miscellaneous symptoms                            |
| Tomatoes (raw) . . . . .    | 2.8                  | Distention, sour stomach, belching, urticaria, nausea, pain, headache     |
| Coffee . . . . .            | 2.6                  | Regurgitation, pain, diarrhea, headache, nausea, vomiting, urticaria      |
| Fish . . . . .              | 2.4                  | Nausea, vomiting, pain, urticaria, headache                               |
| "Meats" . . . . .           | 2.4                  | Headache, distention, nausea, vomiting, pain, constipation                |
| Eggs . . . . .              | 2.4                  | Urticaria, belching, regurgitation, nausea                                |
| Strawberries . . . . .      | 2.4                  | Urticaria   |
| Bread—cereals . . . . .     | 2.4                  | Urticaria, pain, nausea, distention                                       |
| Citrus fruits . . . . .     | 2.0                  | Urticaria, belching, regurgitation  |
| Cheese . . . . .            | 1.4                  | Constipation, belching, nausea  |
| Apples (raw) . . . . .      | 1.4                  | Distention, pain  |
| Cream . . . . .             | 1.4                  | Belching, headache, pain, nausea, distention                              |
| Liver . . . . .             | 1.2                  | Belching, nausea, pain, distention, regurgitation                         |
| Potato (white) . . . . .    | 1.1                  | Regurgitation, vomiting, diarrhea, headache                               |

49 other foods, including raw cabbage and cooked peppers, affected less than 1%

## CELIAC DISEASE AND DIARRHEA.

—The **banana** continues to gain in favor as an essential part of the celiac diet. W. W. Barber (A. M. J. Nursing 36:660 (July) 1936) says that the addition of vitamin B to the diet in the form of ripe banana is important in the recovery of patients with celiac disease. Cow's milk should be eliminated, fats omitted entirely and carbohydrate given only in the form of banana, which is well tolerated. This is possibly due to the type of sugar found in the banana, the soft cellulose, and some enzyme which the banana must contain.

The following meals are examples of those used in a personal case:

### Breakfast:

Ripe banana, mashed fine, chosen when the yellow skin has turned black or brown.

### Noon:

Ripe banana.

### Supper:

Ripe banana, mashed fine, as at breakfast

N. T. Saxl (M. Rec. 143:110 (Feb. 5) 1936) mentions the value of the **banana** in *celiac disease*. It must be ripe. He credits it with containing invert sugar, starch, a small amount of protein, and mineral salts. It has an adequate amount of all vitamins excepting D. There are no intestinal fermentations producing loose stools. He believes that the banana contains some unknown factor which cures the disease.

F. Shippam (Canad. M. A. J. 34:243 (Mar.) 1936) also recommends the **banana**; as many as 8 or 10 may be given daily. The following diet is used for children who are discharged and attend regularly the out-patient department of which he has charge:

### Breakfast:

Lean chicken.

Twice baked or toasted bread.

Whole egg.

Skim protein milk sweetened with saccharine.

### Dinner:

Soup (fat-free or bovril).

Lean chicken.

Twice baked or toasted bread.

Puree of green peas.

Skim milk custard.

Cheese.

Skim protein milk

One banana.

### Supper:

Twice baked or toasted bread.

White fish or finnan haddie.

Skim milk custard.

One banana.

Protein skim milk.

More bananas may be given if patient has not tired of them.

J. D. Boyd (J. Pediat. 8:234 (Feb.) 1936) states that in the treatment of *diarrhea* in childhood, the raw **apple diet** has become popular. At the conclusion of the period the patient receives farina, toast, and cocoa made with water, soup with rice, scraped beef with toast, cottage cheese and ripe banana. C. Loring Joslin (South. M. J. 29:1007 (Oct.) 1936) corroborated the work of some European investigators who have been using the **banana** in feeding cases of *diarrhea* in children and infants, and has found that the banana therapy in forms of raw, fresh, fully ripe or dehydrated or powdered banana was truly beneficial. As soon as the diets are started, the patient has an appreciable reduction in the number of stools, and during the period does not lose as much weight as formerly, and in some cases there is no loss of weight.

**DIABETES.**—P. White (Canad. M. A. J. 35:153 (Aug.) 1936) states that there are many forms of treatment of diabetes, but the fundamental principles and aims are the same, *i. e.*, (1) to maintain weight, or, if the patient is a child, to promote the normal rate of growth and development; (2) to obtain urine practically free from sugar and to keep the blood sugar at normal levels; (3) to

control fat metabolism; and (4) to prevent acidosis.

The dietary treatment of the disease depends upon its severity and the age of the patient. With the average adult diabetic over 50 years of age who is coöperative, treatment has never been so difficult and the ultimate results have been good. The results with the severe and youthful type of diabetes have been less satisfactory and, as a result of this, many types of dietary treatment have been used. These variations are as follows:

1. High carbohydrate, low fat diet.
2. Low carbohydrate, high fat diet.
3. Moderate carbohydrate, moderate fat diet.
4. Low protein diet.
5. High protein diet.
6. Free diet.

At the New England Deaconess Hospital the best results have been obtained for children with the carbohydrate varying from 150 to 250 grams, the ratio of carbohydrate to fat from 2 to 1 or 3 to 1.

The free diet has not met with any success and White says "that the real defeatists are proponents of the free or normal diet."

It is generally agreed today that the average adult over 50 years will maintain a normal weight providing he receives 30 calories per kilogram of body weight and the child will grow at a normal rate if he gets 100 calories per kilogram of body weight during infancy, gradually decreasing until 45 calories per kilogram is used during adolescence and 35 calories per kilogram through active early adult life.

According to W. R. Campbell, A. A. Fletcher and R. B. Kerr (Am. J. M. Sc. 192:589 (Nov.) 1936), many different types of diet have been used on patients being treated with protamine insulin, *i. e.*, the high fat-low carbohydrate, the low fat and high carbohydrate,

and the amount of carbohydrate and fat being equal. It has been found that patients on diets high in fat and moderately low in carbohydrate have responded to treatment more readily with a single large dose of protamine insulin. Diets very high in carbohydrate and low in fat have been less suitable. The writers state that "greater latitude in the amounts of certain foods eaten (meat, fat, and low percentage carbohydrate foods) may be allowed to a patient than when regular insulin alone is used."

**DIET AND TEETH.**—K. Mellanby (Med. Woman's J. p. 38 (Feb.) 1936), in an article on diet, dental disease, and pregnancy, says that some substances are protective and assist in the building up of normal resistant tissues, among which vitamin A and D must be included, whereas other substances, such as cereals, hinder these processes.

The following factors influence calcification:

1. Assisting:
  - Egg yolk.
  - Fish fats.
  - Vitamin D whole milk.
  - Animal fats.
  - Cod-liver oil.
  - Irradiated ergosterol (radiostol).
  - Salts of calcium and phosphorus.
  - Ultraviolet light; irradiation of animal and food.
2. Antagonizing: Cereals.

The diet must be watched throughout life if dental disease is to disappear, but the diet of the pregnant and lactating woman should be of first concern, and then the diet of the young child after weaning. It is recommended that the diet include 1 or 2 pints of milk daily, egg yolk, butter, suet, green vegetables, carrots, and cod-liver oil. Since cereals may be harmful if not enough protective foods are eaten, it is suggested that potatoes be substituted.

In experiments with dogs, it was shown that better teeth resulted when more calcium was included in the diet; when, however, more cereal was given, the tendency to abnormalities was greater. The type of cereal made some difference. Oatmeal and maize had strong anticalcifying properties, and white flour and rice were comparatively weak. The writer claims that it is not the carbohydrate which does the harm, but some factor present in small amounts.

It has also been found that nerves are affected by a vitamin A deficient diet, and the writer believes that vitamin A may play some part in the prevention of pyorrhea, since this disease develops as a result of loss of neurotrophic control.

### INTESTINAL RATE AND NORMAL NUTRITION.—

In discussing intestinal rate, normal nutrition and health, F. L. Burnett (*Am. J. Digest. Dis. and Nutrition* 3: 469 (Sept.) 1936) believes that the rate of digestion of foods has much to do with disease. By studying the dietary habits of individuals and finding the rate of digestion, such conditions as skin diseases and arthritis are cured. He discourages the use of laxatives, eating too fast, eating at irregular hours, eating too much or not enough, and unbalanced meals. If the "food goes through the body instead of into the body," the maximum value of the food is not being received and naturally disease of some tissue or tissues follows and finally breaks down, resulting finally in some metabolic disease. Individuals should be taught to eat and live properly. When the intestinal rate of digestion is normal and normal feces result, the individual will find himself in good health and remain there as long as he follows the rules.

Burnett believes, as do many others, that the intestinal rate is the most exact

way of determining whether nutrition is normal in an individual. The normal rate is determined as follows:

An evening meal is marked by having the patient eat some French millet seeds or 100 Gm. (3½ ounces) of charcoal. It should take about 134 hours to disappear entirely from the feces and should not appear before 62 hours. If a patient under the writer's care does not come up to this normal, he is checked up until he does.

Coöperation is very essential.

Patients are first given instruction about eating habits by being told to eat slowly and regularly; to eat dinner at night; to omit laxatives; eat fruit at lunch and dinner; and to try to deject twice a day.

The following outline is a sample brought in by a patient and criticized:

- 6.30 to 6.50 P. M.—Beef broth, steak, beans, beets, toast, apple sauce, cake.
- 7.00 P. M.—Charcoal taken to mark this meal.

#### *Friday:*

- 7.45 to 8.00 A. M.—Egg, toast, coffee.
- 9.15 A. M.—Soft dejection with first charcoal—initial intestinal rate, 14 hours.
- 12.15 to 12.35 P. M.—Fish chowder, crackers, apple pie.
- 6.30 to 6.55 P. M.—Potato soup, cod, lima beans, broccoli, roll, peaches, cake.

#### *Saturday:*

- 7.00 A. M.—Soft dejection with charcoal.
- 8.00 to 8.20 A. M.—Oatmeal, egg, toast, coffee.
- 1.00 to 1.20 P. M.—Vegetable soup, crackers, carrots, prunes, cake.
- 6.15 to 6.40 P. M.—Bouillon, chicken, potato, squash, spinach, roll, plum tart.

#### *Sunday:*

- 8.30 to 8.50 A. M.—Creamed toast, fish ball, coffee.
- 10.00 A. M.—Soft dejection with last charcoal, final intestinal rate, 63 hours.
- 1.30 to 2.05 P. M.—Beef, potato, parsnips, cauliflower, roll, raspberry ice, cake.
- 6.30 to 6.50 P. M.—Cheese soufflé, vegetable salad, roll, cocoa, peaches, cookies.

*Monday:*

7.30 to 7.45 A. M.—Egg, corn bread, coffee.

9.00 A. M.—Soft dejection without charcoal.

12.30 to 12.50 P. M.—Omelette, potato, blueberries and cake.

6.45 to 7.15 P. M.—Beef, sweet potato, corn, peppers, toast, apple betty.

After examining this record, Burnett observes that it signifies too rapid intestinal rate. The colon is irritable from bad dietary habits and malabsorption is the result. Accordingly, the patient is advised to eat more vegetables, less meat, cereals, and fruits. Other health measures are suggested and the patient is advised to start on a new regime immediately and to return with a report in 2 weeks.

**NUTRITION.**—Probably the most significant work on the problem of nutrition published in 1936 was the Report of the League of Nations, in four volumes. Volume I consists of the *Interim Report of the Mixed Committee on the Problem of Nutrition*:

Discoveries in the past 30 years leading to the "newer knowledge of nutrition" show with ever-increasing certainty that inadequate nutrition plays an important part in infant mortality and can account for the excessive number of underdeveloped school children and adolescents, and the poor health and small output of a large number of workers. Deficiencies in diet and disease of nutritional origin can be observed not only among city population, but also among dwellers in country districts, and not only in poor or primitive countries, but also in rich nations.

On investigation of the existing conditions in every quarter of the globe, it was found that possibly the greater part of humanity may be ill-fed or under-fed.

The diet must supply the necessary substances of growth and repair of

organism, and energy for the production of animal heat and muscular work.

The vitamins, of which about ten have been differentiated, have been called food hormones, the conception being that, in the economy of the body, they direct the correct utilization of the other dietary elements.

The classification of the principal vitamins, all of which are necessary to promote growth and maintain health, is as follows:

*Vitamin A* (Fat-soluble).—Deficiency of vitamin A is shown by certain skin and eye disorders, including night blindness and corneal ulcers leading to total blindness. A high death rate is found in populations deprived of vitamin A, due to infections of the lungs and intestines.

*Vitamin B Complex* (Water-soluble).—The various constituents of this group are concerned with prevention and treatment of beriberi, pellagra, and possibly also of sprue and some forms of anemia.

*Vitamin C* (Water-soluble).—Necessary for the prevention of scurvy.

*Vitamin D* (Fat-soluble).—Necessary for the correct utilization of calcium salts and phosphates in the nutrition of the growing and adult skeleton; for the prevention of rickets, osteomalacia, and dental disease. Vitamin D can be taken in the food as in egg yolk, fish, or liver oils, and it is also synthesized in the skin by the action of certain of the sun's rays which, in the temperate regions, are present only in summer, but are abundant and powerful in their action in tropical and Southern-European countries.

Recent researches have shown the great importance of an adequate amount and correct balance of essential minerals in the diet. Calcium, phosphorus, iron, and iodine are most commonly found, and if these are taken in adequate amounts, the other mineral requirement, such as



magnesium, sodium, sulphur, etc., will be taken care of.

The division of foods into two useful classes has been made: (1) the protective foods—valuable chiefly for providing minerals, vitamins, and “good” protein; (2) the non-protective foods—valuable chiefly as energy-givers. A lack of calories results in starvation, and a lack of protective foods causes various “deficiency” diseases which may develop in spite of an abundant calorie intake.

Table III on following page contains a rough classification of some of the more common types of foods in these two classes and shows their relative value as a source of energy, “good” protein minerals, and the more important vitamins.

The report is divided into sections dealing with the nutrition of the infant, the mother, the school child, the soldier, etc. All of these different types show a tendency to eat more energy and non-protective foods than the protective foodstuffs.

In the diet of the *young infant* there is a common practice now of including cereal and cereal products. “The immediate effect of giving such foodstuffs is often apparently beneficial, as indicated by the increase in weight.” The modern teaching of nutrition is against giving cereal before 8 months or so, and even then only small amounts should be given. Many cereal products are poor in vitamins and available mineral elements, and their inclusion in the diet limits the intake of milk and other protective foods. There is also evidence that they actually are harmful in that they increase the demand for vitamins A and D and calcium, and that their own calcium and phosphorus content are not available for the formation of bone in the growing organism under some circumstances. “Thus a rapidly growing infant nourished with cereals is more liable to suffer from defects of calcification of

the bones and teeth than one on a diet of milk and other protective foods only. It is probable that the consumption of the cereals by these young infants diminishes their resistance to bronchopneumonia, intestinal and other infections.”

A very important problem of child health is the tendency during the school age to contract acute rheumatism, with its tragic associates, *i. e.*, chorea and heart disease (rheumatic endocarditis). “If the greater consumption of protective foods can reduce the distressing condition—and there is some suggestive evidence that it can do so—a great blessing would be conferred on mankind.”

Volume II includes the *Report on the Physiological Bases of Nutrition* drawn up by the Technical Commission of the Health Committee at the meeting held in London (November 25-29, 1935) revised and amplified at the meeting held at Geneva (June 4-8, 1936).

This Report is one which should be of great value to any physician. It includes, first, the energy, protein and fat requirements of the normal individual. The Commission agreed that average values should be used and it is very important that the figures be interpreted in “the light of this fact.”

The *calorie requirements* are first considered. The adult chosen as the average person is one who may be either male or female, living an ordinary life in a temperate climate, and doing *sedentary work*, not manual. An allowance of 2400 calories (amount of energy available from the food actually assimilated) per day is considered adequate to meet the requirements of the above individual.

If an individual is engaged in *heavier work*, the following should be considered as additions to the basic requirements given above.

Light work: up to 75 calories per hour of work.

TABLE III

| Food   | "Good"<br>Protein | Minerals | Vitamins |    |    |     |                               |
|--|-------------------|----------|----------|----|----|-----|-------------------------------|
|  |                   |          | A        | B  | C  | D   |                               |
| Milk.....  | ++                | +++      | +        | +  | +Ø | +Ø  |                               |
| Cheese.....  | ++                | ++       | +        | +  | —  | —   |                               |
| E Eggs.....  | ++                | ++       | +        | ++ | —  | ++  |                               |
| E Liver.....   | ++                | ++       | +        | ++ | —  | +   |                               |
| E Fat fish (herring,<br>etc.).....                           | +                 | .....    | +        | +  | —  | ++  | Highly<br>Protective<br>Foods |
| Green vegetables,<br>salads.....                             | +                 | +++      | +        | +  | ++ | —   |                               |
| Raw fruit, fruit juice.....                                  | .....             | +++      | +*       | +  | ++ | —   |                               |
| E Butter.....  | —                 | —        | +        | —  | —  | +Ø  |                               |
| Cod-liver oil.....   | —                 | —        | +++      | —  | —  | +++ |                               |
| Yeast.....   | +                 | +        | —        | ++ | —  | —   |                               |
| Meat (muscle).....   | +                 | ⊥        | —        | +  | ⊥  | —   |                               |
| Root vegetables,<br>tubers.....                              | .....             | .....    | +*       | +  | +  | —   |                               |
| Legumes (dry peas,<br>lentils).....                          | .....             | .....    | —        | +  | —  | —   |                               |
| E Cereals, bread<br>(whole meal).....                        | +                 | ⊥        | ⊥        | +  | —  | —   | Less<br>Protective<br>Foods   |
| E Cereals, bread<br>(white).....                             | .....             | .....    | —        | —  | —  | —   |                               |
| E Cereals, rice<br>(polished).....                           | .....             | .....    | —        | —  | —  | —   |                               |
| E Nuts.....  | ⊥                 | .....    | —        | ++ | —  | —   |                               |
| E Sugar, jam, honey ..                                       | .....             | .....    | —        | —  | —  | —   | Non-<br>Protective<br>Foods   |
| E Margarine, olive oil<br>and other vege-<br>table oils..... | .....             | .....    | —        | —  | —  | —   |                               |

- E Energy.  
 +++ Very rich.  
 ++ Rich  
 + Present.  
 ⊥ Present in small amounts or traces.  
 — Absent.  
 Ø In summer, when the cows are on pasture.  
 \* If yellow in color.

Moderate work: up to 75 to 150 calories per hour of work.

Hard work: up to 150 to 300 calories per hour of work.

Very hard work: up to 300 calories and upwards per hour of work.

The following table of coefficients is given to determine the energy requirements for other ages and for mothers:

| Age (years)    | Coefficient | Calories |
|----------------|-------------|----------|
| 1 to 2.....    | 0.35        | 840      |
| 2 to 3.....    | 0.42        | 1000     |
| 3 to 5... ..   | 0.5         | 1200     |
| 5 to 7. ....   | 0.6         | 1440     |
| 7 to 9.....    | 0.7         | 1680     |
| 9 to 11. ....  | 0.8         | 1920     |
| 11 to 12.....  | 0.9         | 2160     |
| 12 to 15.....  | 1.0         | 2400     |
| 15 and upwards | 1.0         | 2400     |

The child of 12 to 15 years of age should be given a calorie allowance corresponding to a coefficient of 1, with the supplements given above for various types of activity. The protein requirement should be an allowance of 2.5 grams of protein per kilogram of body weight.

The Committee suggests that the activities of children of both sexes from 5 to 11 years be considered "as equivalent to light work; of boys from 11 to 15 years, as moderate work; and of girls from 11 to 15 upwards, as light work.

| Women         | Coefficient | Calories |
|---------------|-------------|----------|
| Pregnant..... | 1.0         | 2400     |
| Nursing.....  | 1.25        | 3000     |

If the mother is pregnant or not, an allowance must still be made for household duties, which need to be counted as equivalent to light work for 8 hours daily.

The requirements for babies under 1 year are difficult to specify except in terms of body weight as follows:

| Age (Months) | Calories per Kilogram of Body Weight |
|--------------|--------------------------------------|
| 0 to 6.....  | 100                                  |
| 6 to 12..... | 90                                   |

Regarding the protein requirement of all normal individuals, 1 gram of protein per kilogram of body weight is suggested. It is advised that this should be derived from a variety of sources, and that part of the protein should be of animal origin. Animal protein is considered very important during growth, pregnancy, and the lactating period.

The following table gives the protein requirement for different ages:

| Age (Years)            | Grams per Kilogram of Body Weight |
|------------------------|-----------------------------------|
| 1 to 3....             | 3.5                               |
| 3 to 5.....            | 3.0                               |
| 5 to 12.....           | 2.5                               |
| 12 to 15.....          | 2.5                               |
| 15 to 17.....          | 2.0                               |
| 17 to 21.....          | 1.5                               |
| 21 and upwards.....    | 1.0                               |
| Women:                 |                                   |
| Pregnant—0 to 3 months | 1.0                               |
| 4 to 9 months          | 1.5                               |
| Nursing.....           | 2.0                               |

Data concerning the fat requirement is not available. The high vitamin A and D content of certain fats justifies their use in liberal amounts.

Colder climates may mean an increase in energy content for individuals living in them.

The Committee reports that deficiencies of modern diets are not usually in energy content, but rather in protective foods.

The definition of *protective foods* is given as follows: "The term, protective food, denotes a foodstuff which is especially rich in those nutrient principles, 'good' protein, vitamins or minerals, on which the principal foods of any geographic area are deficient."

An example is given in the United States of America, where the chief constituents of the daily diet are usually white bread and other foods made from white flour and sugar. Muscle, meats, milk and the leafy vegetables form the most important protective foods.

The protective foods listed are "first, and most important, milk and milk products (including butter), eggs and glandular tissues, then green leaf vegetables, fruit, fat, fish and meat (muscle). Among the energy-bearing foods of little or no protective power are sugar, milled cereals, and certain fats."

Regarding requirements for *pregnancy* and *lactation*, the Commission has attempted to "define the quantitative needs of protective foods for perfect nutrition in terms of the requirements for the pregnant and nursing woman. She should be regarded as the member of the population needing the greatest 'protection' in order to ensure the adequate physical endowment for the child at birth and optimum nutrition during infancy." The most difficult problem in these diets is to guarantee sufficient amounts of calcium, phosphorus, iron, and vitamins B, B<sub>1</sub>, B<sub>2</sub>, C and D.

The following foods are recommended and reasons given:

Whole milk or skimmed milk is considered a very rich source of calcium salts, phosphorus, and of vitamin B<sub>2</sub>, and B<sub>1</sub>.

Milk fat contains vitamin A.

The egg is rich in vitamin A, B<sub>1</sub>, B<sub>2</sub> and D, and also in iron.

The proteins of milk and eggs are the best types of protein available, and

also improve the utilization of protein contained in cereals and vegetables.

Milk improves the utilization of vitamin D from other sources because of its calcium and phosphate salts. It also renders more effective the iron contained in other foods in the diet, even though it is a very poor source itself.

Cod-liver oil or other fish oils rich in vitamin D are recommended in the diet of pregnant and nursing mothers, also in the diet of the growing child. They are also the richest known natural source of iodine and vitamin A.

Potatoes are suggested in the diet to replace sugar used for energy and the highly refined cereals. Potatoes provide extra vitamin C and more readily available calcium and phosphorus than is found in cereals. The yield of vitamin B and iron is important. Of course, potatoes are recommended to appear in abundance in the diet of peoples in countries where the potato is plentiful.

Breast feeding is recommended during the first 8 or 9 months of the life of the *infant*.

The infant should always, without exception, receive additions to his diet, such as fresh fruit or vegetable juice, to provide vitamin C for its antiscorbutic properties, and a small daily ration of cod-liver oil for vitamin D when sunshine is not abundantly available.

When artificial feeding must be resorted to, the basis of the diet should be milk, supplemented by adequate amounts of vitamin A, C, and D. The milk used should always be pasteurized or raised to the boiling point, to prevent the danger of any infection.

Since nature supplies the infant with only enough iron to last for 6 months, the reserve is soon exhausted and must be supplied daily in the diet. Since milk is deficient in this mineral, the diet of all infants should be supplemented with egg yolk, or purées of green vegetables

| A. Protective Foods   | Amount | Protein Grams | Calcium    |     | Phosphorus | Iron     | Iodine         | Vitamin A           |                 | Vitamin B1 | Vitamin B2 | Vitamin C | Vitamin D        | Calories | Remarks   |
|---|--------|---------------|------------|-----|------------|----------|----------------|---------------------|-----------------|------------|------------|-----------|------------------|----------|---|
|   |        |               | Milligrams |     |            |          |                | International Units |                 |            |            |           |                  |          |   |
| Milk.....   | 1,000  | 32            | 1.2        | 0.9 | 2.4        | 0.02     |                | Rich (1000-3000)    | Good (50-75)    | Rich       | Poor       | Poor      | Poor             | 660      | (a) Calculations for lean meat                                  |
| Meat (or fish or poultry)....                                     | 120(a) | 22            |            | 0.3 | 5.0        |          |                | Poor                | Poor (b)        | Rich       | Poor       | Poor      | Poor             | 240      | (a <sub>1</sub> ) One-half calculated as available iron         |
| Eggs (1).....   | 50     | 6             |            | 0.1 | 1.5        |          |                | Rich (1000-1300)    | Good (about 15) | Rich       | Rich       | None      | 25-40            | 70       | (b) Except glands (liver and kidneys) and pork muscle           |
| Cheese (c).....   | 30     | 8             | 0.3        | 0.2 | 0.4        |          |                | Rich (800-1000)     | Poor            | Good       | Good       | Poor      | Poor             | 125      | (c) Calculated as cheddar cheese                                |
| Green and leafy vegetables..                                      | 100(a) | 1             | 0.1        |     | 1.2        |          |                | Rich (1000-1500)    | Good            | Good       | Good       | Poor      | None             | 30       | (d) Estimated on basis of 1/8 cabbage, 1/8 lettuce, 1/8 spinach |
| Potatoes.....   | 250    | 6             |            | 0.2 | 2.0        |          |                | Poor                | Good            | Good       | Good       | Good      | None             | 250      | (e) Calculated as beans   |
| Legumes, dried..  | 10(e)  | 2             |            |     | 0.2        |          |                | Poor                | Good            | Good       | Good       | None      | None             | 35       | (f) Calculated as white flour                                   |
| Cod-liver oil. . . .  | 3.5    |               |            |     |            |          | Richest source | Rich (1800-3500)    | None            | None       | None       | None      | Rich (about 300) | 30       | (g) Calculated as whole wheat flour                             |
| An available source of vitamin C (from raw fruits and vegetables) |        |               |            |     |            |          |                |                     |                 |            |            |           |                  |          |   |
| Total yield.....  |        | 77            | 1.6        | 1.7 | 10.2       | Adequate |                | Over 5000           | Over 150        | Adequate   | Over 500   | About 300 |                  | 1440     |   |

B. Supplementary Energy-yielding Foods by Means of Which the Individual's Energy Requirements Can Be Met.

|                                   |        |    |     |     |     |  |  |  |                  |  |  |  |  |  |  |
|-----------------------------------|--------|----|-----|-----|-----|--|--|--|------------------|--|--|--|--|--|--|
| Cereals as needed.....            | 250(f) | 28 |     | 0.2 | 2.5 |  |  |  |                  |  |  |  |  |  |  |
| Highly milled or whole grain..... | 250(g) |    | 0.1 | 0.9 | 9.0 |  |  |  | Rich (about 250) |  |  |  |  |  |  |

\* The estimates are based on data in Sherman's "CHEMISTRY OF FOOD AND NUTRITION", 4th edit., 1933. The figures for milk are calculated for a content of 3.2% protein and 3.5% fat. The figures for vitamins, however, are converted to international units and must be regarded as rough approximation only.

or carrots, or in very severe cases of deficiency, by iron salts ordered by the physician.

For *premature infants*, supplementary vitamin and mineral additions should be given in the very first days after birth. Artificial vitamin D concentrates, however, should only be under medical supervision, in order to prevent overdosage.

The Committee does not advise giving cereal foods before the age of 6 months, and suggests that potatoes be used in

place or partly in place of cereals after this period. The reason for this is referred to in another section of this report.

Fat in the diet of the infant must be given very carefully. Too much may cause gastric upset and fat intolerance. The 3 to 3.5 per cent. of fat contained in milk is generally considered sufficient.

The following tables are included as very fine examples of the adequate nutritional requirements of children of ages 1 to 14 years, as arranged by the above Committee.

TABLE IV  
*Children, age 1 to 2 years (840 Calories)*

| Food  | Amount (Grams) | Calories | Protein (Grams) |
|---|----------------|----------|-----------------|
| A. Protective Foods:  |                |          |                 |
| Milk.....   | 750            | 490      | 24              |
| Egg (1) (or equivalent as 30 grams meat, fish, or liver, if available)..... | 48             | 70       | 6               |
| Green leafy vegetables.....   | 30-60          | 15       | ....            |
| Potato (or carrot).....   | 30             | 30       | ....            |
| Cod-liver oil.....  | 3              | 30       | ....            |
|   |                | 635      | 30              |
| B. Supplementary Energy-yielding Foods:                                     |                |          |                 |
| Fats (butter, if possible).....   | 7              | 50       | ....            |
| Cereals (calculated as bread).....  | 50             | 150      | 7               |
|   |                | 835      | 37              |

TABLE V  
*Children, age 2 to 3 years (1000 Calories)*

| Food  | Amount (Grams) | Calories | Protein (Grams) |
|---|----------------|----------|-----------------|
| A. Protective Foods:  |                |          |                 |
| Milk.....   | 1000           | 660      | 32              |
| Egg (1) (or equivalent as 30 grams meat, fish, or liver, if available)..... | 48             | 70       | 6               |
| Green leafy vegetables.....   | 30-60          | 15       | ....            |
| Potato (and other root vegetables).....                                     | 50             | 50       | 1               |
| Cod-liver oil.....  | 3              | 30       | ....            |
| A source of vitamin C (raw vegetable or fruit)                              |                | 825      | 39              |
| B. Supplementary Energy-yielding Foods:                                     |                |          |                 |
| Fats (butter if possible).....  | 10             | 75       | ....            |
| Cereals (calculated as bread).....  | 50             | 150      | 7               |
| Total.....  |                | 1050     | 46              |

TABLE VI  
*Children, age 3 to 5 years (1200 to 1300 Calories)*

| Food  | Amount<br>(Grams) | Calories | Protein<br>(Grams) |
|---|-------------------|----------|--------------------|
| A. Protective Foods:  |                   |          |                    |
| Milk.....   | 1000              | 660      | 32                 |
| Egg (1) (or equivalent as 30 grams meat, fish, or liver, if available)..... | 48                | 70       | 6                  |
| Green leafy vegetable.....  | 60-100            | 20       | 2                  |
| Potato (and other root vegetables).....                                     | 100               | 100      | 2                  |
| Cod-liver oil.....  | 3                 | 30       | ....               |
| A source of vitamin C (raw vegetable or fruit)                              |                   |          |                    |
|   |                   | 880      | 42                 |
| B. Supplementary Energy-yielding Foods:                                     |                   |          |                    |
| Fats (butter, if possible).....   | 15                | 110      | ....               |
| Cereal (calculated as bread).....   | 75                | 225      | 11                 |
| Total.....  |                   | 1215     | 53                 |

TABLE VII  
*Children, age 5 to 7 years (1400 Calories)*

| Food   | Amount<br>(Grams) | Calories | Protein<br>(Grams) |
|--|-------------------|----------|--------------------|
| A. Protective Foods:                           |                   |          |                    |
| Milk.....                                      | 1000              | 660      | 32                 |
| Egg (1).....                                   | 48                | 70       | 6                  |
| Meat, fish, liver, or cheese.....              | 30                | 40       | 6                  |
| Green leafy vegetables.....                    | 100               | 30       | 3                  |
| Potato (and other root vegetables).....        | 150               | 150      | 3                  |
| Cod-liver oil.....                             | 3                 | 30       | ....               |
| A source of vitamin C (raw vegetable or fruit) |                   |          |                    |
|  |                   | 980      | 50                 |
| B. Supplementary Energy-yielding Foods:        |                   |          |                    |
| Fats (butter, if possible).....                | 20                | 150      | ....               |
| Cereals (calculated as bread).....             | 100               | 300      | 14                 |
| Total.....                                     |                   | 1430     | 64                 |

TABLE VIII

Children, age 12 to 14 years  $\left\{ \begin{array}{l} 3200 \text{ Calories (boys)} \\ 2600 \text{ Calories (girls)} \end{array} \right.$

| Food  | Amount<br>(Grams) | Calories | Protein<br>(Grams) |
|---|-------------------|----------|--------------------|
| A. Protective Foods:  |                   |          |                    |
| Milk...   | 1000              | 660      | 32                 |
| Egg (1) . . . . .   | 48                | 70       | 6                  |
| Meat, fish, liver, or cheese . . . . .  | 90                | 120      | 18                 |
| Green leafy vegetables . . . . .  | 250               | 75       | 7                  |
| Potato (and other root vegetables) . . . . .  | 300               | 300      | 6                  |
| Cod-liver oil . . . . .   | 3                 | 30       | .                  |
| A source of vitamin C (raw vegetable or fruit)  |                   |          |                    |
|   |                   | 1255     | 69                 |
| B. Supplementary Energy-yielding Foods:   |                   |          |                    |
| Fats (butter, if possible), cereals, and other foods furnish the total calories required. |                   |          |                    |

**PEPTIC ULCER.**—Since there has been much criticism of the Sippy regime in the treatment of peptic ulcer, P. H. Wosika (Am. J. Digest. Dis and Nutrition 3:419 (Aug.) 1936) made a study to determine the value of tablets composed of powdered whole milk and varying amounts of alkalis on the neutralization of gastric acidity in patients with peptic ulcer compared with the usual Sippy diet. The objections made to cow's milk were that it may contain bacteria, and the hard curd produced may cause spasm of the pylorus, thereby causing distress. The tablets were composed of **powdered whole milk** (12.5 Gm.), **sodium bicarbonate** (0.6 Gm.), and **calcium carbonate** (2.0 Gm.) and were found to be slightly more effective in producing neutralization of the gastric juice than the Sippy routine.

F. Kellogg and S. R. Mettier (Arch. Int. Med. 58:278 (Aug.) 1936)) discuss the effect of alkaline therapy for peptic ulcer on the utilization of dietary iron. He advises that the diet be supplemented by **foods containing iron**, and that 12 to 15 mg. iron be given in this manner. Mettier, Kellogg and Rinehart

have shown that the daily administration of a meal predigested with **pepsin** and **hydrochloric acid** and containing 12 to 15 mg. of iron causes a rapid and satisfactory concentration of hemoglobin in patients with idiopathic hypochromic anemia. Accordingly, cooked eggs, spinach, and scraped beef containing from 12 to 15 mg. were given daily. **Vitamin C** was provided by the ingestion of small amounts of orange juice. It was demonstrated that an iron-rich diet had practically no effect on the formation of hemoglobin during the period that the patient was being alkalinized, but that after the alkalis were stopped, it had a marked effect comparable to that produced by adequate therapy with inorganic iron.

**RENAL DISORDERS.**—R. S. Reeves (Pennsylvania M. J. 40:10 (Oct.) 1936) believes that diet must be rigid in the treatment of *acute nephritis*. Bland foods, low in calories, with a strict restriction of protein and salt content, high in carbohydrates, with fluid intake not over 1000 c.c. and low fat intake, are the most important principles in *the*



*treatment.* The writer states that these patients are "grateful for orangeade, lemonade, milk, weak tea, fruits, and starchy materials such as gruels, corn-starch, sugar, honey, and potatoes."

During the later stages the following is suggested:

Breakfast:

- 1 sliced orange.
- 1 medium slice of toast with 1 square of butter.
- 1 cup of coffee.
- 1 teaspoonful of sugar and 1 tablespoon of cream.

Luncheon:

- 6 tablespoons of cream of wheat with butter.
- 3 tablespoons of buttered carrots.
- Pineapple and marshmallow salad with cream dressing.
- 1 slice of whole wheat bread.
- $\frac{1}{2}$  tablespoon of butter.
- 1 glass of milk.

Dinner:

- Medium-sized tomato and lettuce.
- 4 tablespoonfuls of string beans.
- 1 medium slice of bread with 1 square of butter.
- 1 helping of apple tapioca pudding with 2 tablespoons of cream.
- 1 glass of milk.

The above diet contains about 31 grams of protein.

The infection causing the condition will decide the diet for *nephrosis* or *tubular nephritis*. The edema receives the most attention. Edema is caused by a fall in osmotic pressure which, Reeves explains, depends upon albumin more than globulin, because the albumin molecule is one-third the size of the globulin molecule. Normally there are twice as many albumin as globulin molecules. The number and not the size determines the osmotic pressure. Greater loss of albumin is found in the urine, since a small molecule gets into the urine more easily than a larger one.

The normal protein in the blood should be 6.7 grams per 100 c.c. A fall of a

gram, bringing it below 5 grams, means that almost all of the albumin is gone and edema will result. The maintenance  $\frac{2}{3}$  gram of protein per kilogram of body weight is not sufficient to meet this demand and must be raised. A high protein diet should be prescribed, *i. e.*, one containing between 100 and 200 grams of protein per day. The salt should also be restricted and fluids limited to 1000 c.c. for 24 hours.

The dietary treatment for *hypertension* which Reeves suggests, is a sensible one. He believes that treatment of each person as an individual is necessary. Protein must not be reduced, since in many cases secondary anemia is produced. Weight must not be increased, in order to save the heart extra work. The amount of salt and protein is influenced by the findings of the renal function and blood chemistry.

If tests show that renal function is normal, the protein intake is safe at about 75 grams per day. To protect the nervous system, no stimulants or irritants should be used.

If conditions call for salt restriction the 2-grams salt diet, or low salt, or as it sometimes is called, salt-poor diet is in order. The following day's menus suggest a day's dietary containing about 75 grams of protein and 2 grams of salt. Unsalted butter must be used.

Breakfast:

- $\frac{1}{2}$  orange.
- 2 heaping tablespoons of cereal.
- 1 soft boiled egg.
- 1 slice of toasted wholewheat bread.
- 1 cup of coffee with 1 teaspoon of sugar and 1 tablespoon of cream.

Luncheon:

- 1 scrambled egg served in broiled tomato.
- 3 tablespoons of buttered carrots.
- 1 slice of canned pineapple with cream dressing.
- 1 toasted bran muffin.
- 1 graham cracker.
- 1 glass of milk.

## Dinner:

- 1 slice of broiled beefsteak.
- 2 tablespoons of green peas.
- 2 tablespoons of beets.
- 1 helping of lettuce and tomato salad with French dressing.
- 1 slice of bread.
- 4 tablespoons of cup custard.
- 1 glass of milk.

Fluids may be used up to 6 quarts per day before the blood-pressure is influenced.

In the dietetic treatment of *uremia*, Reeves (*Ibid.*) states that increase of the fluid intake to the greatest possible degree is of utmost importance. During the first 24 hours, he suggests that the intake be 4000 c.c. and 3000 c.c. be maintained as the daily intake after the first 24 hours. If the blood urea nitrogen reading is 65 mg. per 100 c.c. or over, the protein must be reduced to about 20 to 25 grams per day, and the carbo-

hydrate increased to make up the calories. Fat must be limited because these patients sometimes vomit a great deal.

For *pyelitis* and *pyelonephrosis*, the dietetic treatment calls for easily digested foods such as orange juice, stewed fruits, soft cooked or poached eggs, milk, toast, bread and butter, preserves, and simple desserts, such as junket and custards. Alcohol is forbidden.

The following foods are suggested as *renal irritants* and should be avoided in individuals with urogenital tract involvement due to tuberculosis, malignancy or traumatism: Alcohol, condiments, artichokes, asparagus, Brussels sprouts, cabbage, cauliflower, cucumber, charged beverages, leeks, purine bases, onions, pickles, radishes, rhubarb, scallions, watercress, and shell fish.

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